DISSERTATION ON

A STUDY ON THE ASSOCIATION BETWEEN DEHYDROEPIANDROSTERONE AND FRAILTY IN ELDERLY

submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

in partial fulfillment of the regulations
for the award of the degree of

M.D., IN GERIATRIC MEDICINE

BRANCH – XVI

DEPARTMENT OF GERIATRIC MEDICINE
MADRAS MEDICAL COLLEGE
CHENNAI – 600 003

APRIL 2015

CERTIFICATE

This is to certify that the dissertation titled **"A STUDY ON THE ASSOCIATION BETWEEN DEHYDROEPIANDROSTERONE AND FRAILTY IN ELDERLY"** is a bonafide work by **Dr. P.ARAVIND BABU,** Post Graduate student, Department Of Geriatric Medicine, Madras Medical College, Chennai, in partial fulfillment of the requirements for M.D., DEGREE in GERIATRIC MEDICINE, BRANCH – XVI Examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, under our guidance and supervision, during the academic period from April 2012 to April 2015.

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DECLARATION

I, **Dr. P.ARAVIND BABU,** solemnly declare that the dissertation titled **"A STUDY ON THE ASSOCIATION BETWEEN DEHYDROEPIANDROSTERONE AND FRAILTY IN ELDERLY"** was done by me at Madras Medical College, Chennai – 600 003, during the study period from June 2014 to August 2014, under the guidance and supervision of **Prof. Dr. S.SIVAKUMAR M.D., D.T.R.D.,** Head of Department, Department of Geriatric Medicine, to be submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai towards partial fulfillment of the requirements for the award of M.D., DEGREE in GERIATRIC MEDICINE, BRANCH – XVI.

Place : Chennai.
Date : 24-09-2014.

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INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

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CERTIFICATE OF APPROVAL

To
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Dear Dr. P. Aravind Babu,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"A STUDY ON THE ASSOCIATION BETWEEN DEHYDROEPIANDROSTERONE AND FRAILTY IN ELDERLY"** No.38062014

The following members of Ethics Committee were present in the meeting held on 03.06.2014 conducted at Madras Medical College, Chennai-3.

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11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

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INTRODUCTION

Frailty is a common geriatric syndrome that embodies an increased risk of catastrophic declines in health and function among older adults. Frailty is a condition associated with aging, and it has been recognized for centuries. As described by Shakespeare in *As You Like It*, "the sixth age shifts into the lean and slippered pantaloon, with spectacles on nose and pouch on side, his youthful hose well saved, a world too wide, for his shrunk shank". The shrunk shank is a result of loss of muscle with aging. It is also a marker of a more widespread syndrome of frailty, with associated weakness, slowing, decreased energy, lower activity, and, when severe, unintended weight loss.

Estimates of frailty prevalence in older populations may vary according to a number of factors, including the setting in which the prevalence is being estimated (e.g., nursing home (higher prevalence) vs. community (lower prevalence)), and the operational definition used for defining frailty. Using the widely used frailty phenotype framework proposed by Fried et al (2001), prevalence estimates of about 7-16% have been reported in non-institutionalized, community-dwelling older adults.

The occurrence of frailty increases exponentially with advancing age, and is more common in older women than men, and among those of lower socio-economic status. Frail older adults are at high risk for major adverse health

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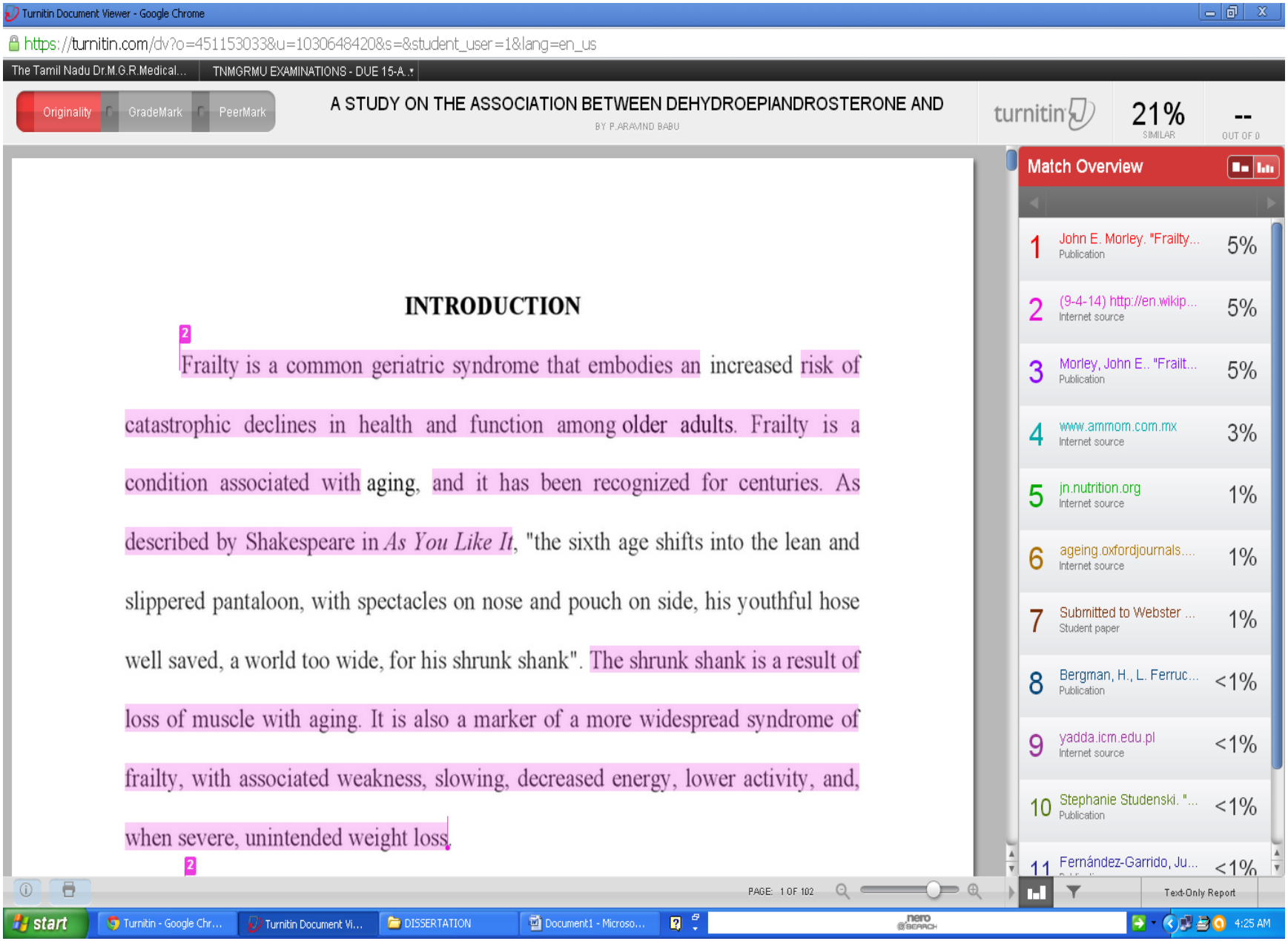
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CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF CHARTS

LIST OF ABBREVIATIONS

DHEA	-	Dehydroepiandrosterone
DHEA-s	-	Dehydroepiandrosterone Sulfate
IGF-1	-	Insulin-Like Growth Factor-1
IL-6	-	Interleukin-6
CRP	-	C-Reactive Protein
CHF	-	Congestive Heart Failure
LPS	-	Lipopolysaccharide
TNF- α	-	Tumour Necrosis Factor-Alpha
DEXA	-	Dual-Energy X-Ray Absorptiometry
CT	-	Computed Tomography
MRI	-	Magnetic Resonance Imaging
GLUT	-	Glucose Transporter
SARM	-	Selective Androgen Receptor Modulator
MGF	-	Mechano Growth Factor
CNTF	-	Ciliary Neuro Trophic Factor
FI	-	Frailty Index
CES-D	-	Centre for Epidemiological Study – Depression scale
PUFA	-	Polyunsaturated Fatty Acid
WHAS	-	Women's Health and Aging Studies
NAD	-	Nicotinamide Adenine Dinucleotide
SIRT1	-	Silent mating-type Information Regulation 1
SULT2A1	-	Sulfotransferase
DHT	-	Dihydrotestosterone
ER	-	Estrogen Receptor
PPAR- α	-	Peroxisome Proliferator-Activated Receptor-Alpha

PXR	-	Pregnane X Receptor
CAR	-	Constitutive Androstane Receptor
NMDA	-	N-methyl-D-aspartate
GABA	-	Gamma Aminobutyric Acid
11β-HSD1	-	11β-Hydroxysteroid Dehydrogenase
IGFBP1	-	Insulin-Like Growth Factor-Binding Protein 1
ACTH	-	Adrenocorticotropic hormone
CLIA	-	Chemi Luminescence Immunoassay
BPH	-	Benign Prostatic Hyperplasia
HDL	-	High Density Lipoprotein
PCOS	-	Polycystic Ovarian Syndrome
GH	-	Growth Hormone
HSP70	-	Heat Shock Protein 70
TGF-β	-	Transforming Growth Factor-Beta
LTA	-	Leisure Time Activity
BMI	-	Body Mass Index
SD	-	Standard Deviation
ANOVA	-	Analysis Of Variance.

A STUDY ON THE ASSOCIATION BETWEEN DEHYDROEPIANDROSTERONE AND FRAILTY IN ELDERLY

AUTHOR: Prof. Dr. S.SIVAKUMAR, **Dr. P.ARAVIND BABU**,

Madras Medical College & RGGGH, Chennai – 600003.

BACKGROUND: The biological basis for Frailty remains unclear. It is hypothesized that loss of bone mass, decline in protein synthesis, sarcopenia and immune dysfunction influence the onset of frailty. Studies show that low serum DHEA levels are associated with increased rates of morbidity and mortality. Serum levels of DHEA decline with age, and this decline is paralleled by a decrease in muscle and bone mass. Hence we take up this study to test the hypothesis that declining serum DHEA is associated with the frailty phenotype.

AIMS & OBJECTIVES: To evaluate the association between Dehydroepiandrosterone (DHEA) and Frailty in the elder population.

METHODS: The study group includes elderly subjects > 65 yrs, in the Geriatric ward of Rajiv Gandhi Govt. General Hospital, Chennai, who complied with the inclusion and exclusion criteria. Anthropometric evaluation was done. **Fried's criteria** was employed to assess the frailty phenotype. Patients were categorized into 3 groups based on the number of frailty components - FRAIL (≥ 3 characteristics); INTERMEDIATE FRAIL (1-2 characteristics); NON-FRAIL (no characteristic). Blood samples of patients from each group were collected for

estimating serum DHEA-s level (using CLIA method) and analysis was performed by appropriate statistical methods.

RESULTS: In a study conducted in 100 participants, a significant association between Frailty phenotype and DHEA level was observed (**p < 0.0004**). Ordinal logistic regression was used to model the relationship between frailty and DHEA, adjusting for age, gender and BMI. A significant DHEA–BMI interaction (OR=1.09; 95% CI; **p = 0.0001**) suggested that, in general, the relationship between higher levels of frailty decreased relative to higher levels of DHEA, but the magnitude of decrease was larger at lower BMI values and smaller at higher BMI values. A BMI >29 kg/m² attenuated the association between DHEA levels and frailty.

CONCLUSION: This study found an inverse association between frailty and DHEA-s levels, similar to other studies that have found associations between DHEA-s and physical function. Whether the inverse association is due to similar conditions resulting in lower DHEA levels and more susceptibility to frailty or whether lower DHEA levels have an impact on increasing frailty cannot be addressed by this cross-sectional analysis.

KEYWORDS: Frailty, Dehydroepiandrosterone sulphate (DHEA-s), Fried's criteria, Body Mass Index (BMI)

INTRODUCTION

Frailty is a common geriatric syndrome that embodies an increased risk of catastrophic declines in health and function among older adults. Frailty is a condition associated with aging, and it has been recognized for centuries. As described by Shakespeare in *As You Like It*, "the sixth age shifts into the lean and slippered pantaloon, with spectacles on nose and pouch on side, his youthful hose well saved, a world too wide, for his shrunk shank". The shrunk shank is a result of loss of muscle with aging. It is also a marker of a more widespread syndrome of frailty, with associated weakness, slowing, decreased energy, lower activity, and, when severe, unintended weight loss.

Estimates of frailty prevalence in older populations may vary according to a number of factors, including the setting in which the prevalence is being estimated e.g., nursing home (higher prevalence) vs. community (lower prevalence), and the operational definition used for defining frailty. Using the widely used frailty phenotype framework proposed by Fried et al (2001), prevalence estimates of about 7-16% have been reported in non-institutionalized, community-dwelling older adults.

The occurrence of frailty increases incrementally with advancing age, and is more common in older women than men, and among those of lower socio-economic status. Frail older adults are at high risk for major adverse health

outcomes, including disability, falls, institutionalization, hospitalization, and mortality.

Epidemiologic research to date have led to the identification of a number of risk factors for frailty, including: (a) chronic diseases, such as cardiovascular disease, diabetes, chronic kidney disease, depression, and cognitive impairment; (b) physiologic impairments, such as activation of inflammation and coagulation systems, anemia, atherosclerosis, autonomic dysfunction, hormonal abnormalities, obesity, hypovitaminosis-D in men, and environment-related factors such as life space and neighborhood characteristics. Advances about potentially modifiable risk factors for frailty now offer the basis for translational research effort aimed at prevention and treatment of frailty in older adults.

Recent work on frailty has sought to characterize both the underlying changes in the body and the manifestations that make frailty recognizable. It is well-agreed upon that declines in physiologic reserves and resilience is the essence of being frail. Similarly, scientists agree that the risk of frailty increases with age and with the incidence of diseases. Beyond that, there is now strong evidence to support the theory that the development of frailty involves declines in energy production, energy utilization and repair systems in the body, resulting in declines in the function of many different physiological systems. This decline in multiple systems affects the normal complex adaptive behavior that is essential to

health and eventually results in frailty typically manifesting as a syndrome of a constellation of weakness, slowness, reduced activity, low energy and unintended weight loss. When most severe, i.e. when 3 or more of these manifestations are present, the individual is at a high risk of death.

BIOLOGICAL UNDERPINNINGS

It has been suggested that the biological underpinnings of frailty are multifactorial, involving dysregulation across many physiological systems. A pro-inflammatory state, sarcopenia, osteoporosis, anemia, relative deficiencies in anabolic hormones (androgens and growth hormone) and excess exposure to catabolic hormones (cortisol), insulin resistance, compromised altered immune function, micronutrient deficiencies and oxidative stress are each individually associated with a higher likelihood of frailty. Additional findings show that the risk of frailty increases with the number of dysregulated physiological systems in a nonlinear pattern, independent of chronic diseases and chronologic age, suggesting synergistic effects of individual abnormalities that on their own may be relatively mild. The clinical implication of this finding is that interventions that affect multiple systems may yield greater, synergistic benefits in prevention and treatment of frailty than interventions that affect only one system.

Associations between specific disease states are also associated with and frailty have also been observed, including cardiovascular disease, diabetes mellitus, renal insufficiency and other diseases in which inflammation is prominent. To the extent that dysregulation across several physiologic systems underlie the pathogenesis of the frailty, specific disease states are likely concurrent manifestations of the underlying impaired physiologic function and regulation. It is possible that clinically measurable disease states can manifest themselves or be captured prior to the onset of frailty. No single disease state is necessary and sufficient for the pathogenesis of frailty, since many individuals with chronic diseases are not frail. Therefore, rather than being dependent on the presence of measurable diseases, frailty is an expression of a critical mass of physiologic impairments.

It has been recently demonstrated that serum levels of single hormones such as testosterone, DHEA-s, and IGF-1 are predictors of metabolic syndrome, frailty and mortality. Evidence in support of the hypothesis that aging is associated with dysregulation of different components of the homeostatic network is emerging rapidly, especially for biomarkers of inflammation and nutritional status. Through studying the relationship between and among elements of this paradigm, we will better understand the age-related pathway to frailty and progressive disability.

Little is known about the physiological role of DHEA, but human epidemiological studies have suggested that its concentrations may represent a biomarker of successful ageing. Studies show that low serum DHEA levels are associated with increased rates of morbidity and mortality. Serum levels of DHEA decline with age, and this decline is paralleled by a decrease in muscle and bone mass[1,2,3].

Hence we take up this study to test the hypothesis that declining serum DHEA is associated with the frailty phenotype.

AIMS AND OBJECTIVES

To evaluate the association between Dehydroepiandrosterone (DHEA) and Frailty in the elder population.

REVIEW OF LITERATURE

The Geriatric syndrome of Frailty is defined as a loss of reserve and is characterized by weight loss, fatigue, weakness and vulnerability to adverse events, which predict increased morbidity and mortality. It has been hypothesized that loss of bone mass, decline in protein synthesis, sarcopenia and immune dysfunction influence the onset of frailty[4,5].

FRAILTY AS A SYNDROME

Geriatricians have long been aware of a syndrome of multiple coexisting conditions, weakness, immobility, and poor tolerance to physiologic or psychologic stressors. People so affected are often characterized as “frail” and are known to be more vulnerable to poor health outcomes, including disability, social isolation, and institutionalization. Although frailty is more prevalent in older people and in those with multiple medical conditions, it can exist independently of age, disability, or disease, and may be an independent physiologic process involving multiple systems.

DEFINITIONS OF FRAILTY

Frailty represents a form of predisability. In 1990, Fretwell stated “frailty in an individual is defined as an inherent vulnerability to challenge from the

environment.” Because of the high-risk status of frail older adults, geriatric medicine seeks to intervene in frail patients to prevent or minimize illness and dependency. In 1992, a conference on the physiologic basis of frailty agreed that controversy on definition and limited understanding of etiology hindered preventive strategies. In 1993,W. Bortz stated that a major threat to active life expectancy is the development of frailty. Baltes and Smith observed that the oldest old, those in the “fourth age” after 85 years (in developed countries), are particularly biologically vulnerable and frail and have compromised ability to tolerate stressors. As a result, their well-being is increasingly dependent on the use of extrinsic compensations to maintain life and autonomy, because there is such diminished ability to compensate physiologically. These observations frame the conceptual understanding that aging is associated with increased likelihood of frailty, and that older persons have reduced physiological reserve than younger persons and these changes are likely independent of disease. In 2001, Frailty has been objectively defined by Linda Fried and her colleagues at John’s Hopkins University. Their definition includes weight loss, exhaustion, weakness, walking speed, and low physical activity[6]. By this definition, approximately 6.9% of the older population are frail. Females are more often classified as frail than are males of the same age. Frailty is the beginning of a cascade that leads to functional deterioration, hospitalization, institutionalization, and death.

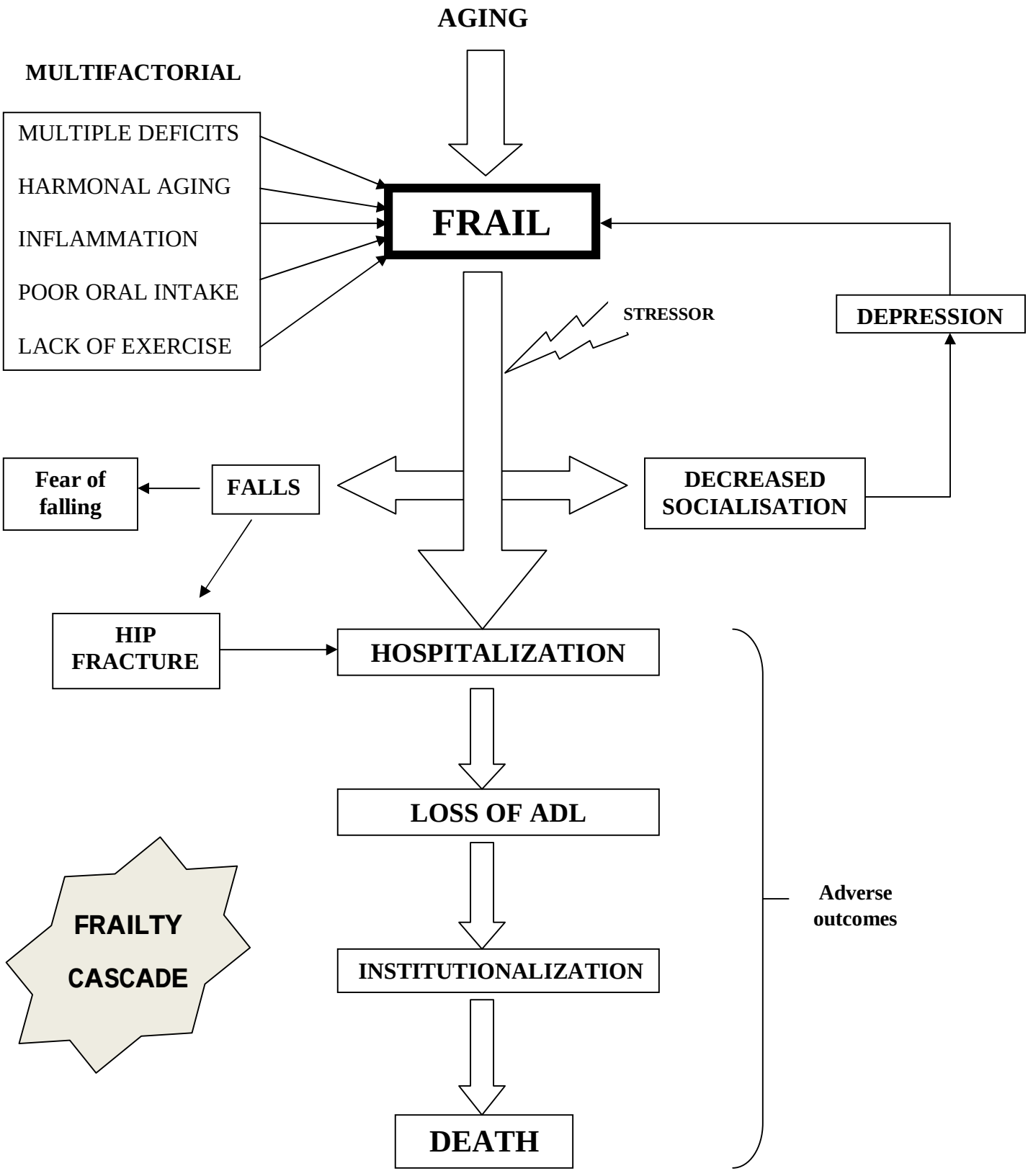


Figure 1 **- FRAILTY CASCADE**

Frailty is the most problematic expression of population ageing. It is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime. This cumulative decline depletes homoeostatic reserves until minor stressor events trigger disproportionate changes in health status.

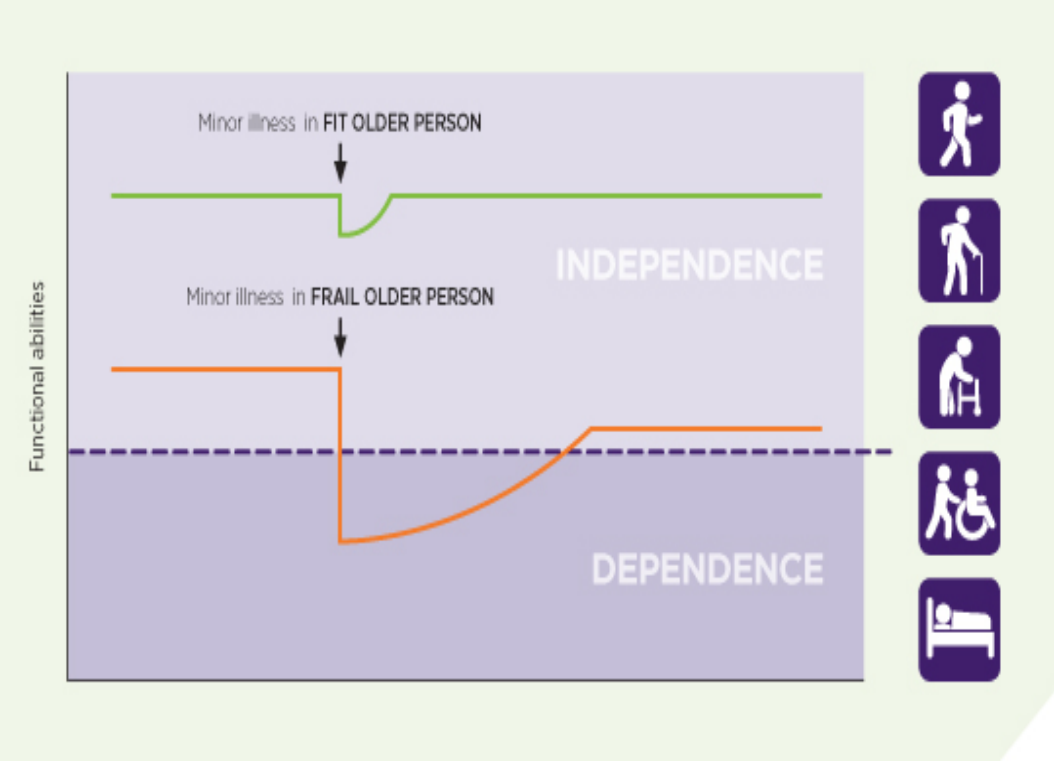


Figure 2 - **FRAILTY & DEPENDENCY**

The picture depicts the varied resilience of a fit and frail elder person to stress.

FRAILTY IS AT THE CORE OF GERIATRIC MEDICINE

1) Frail older persons are at risk for multiple adverse health outcomes including

    a) Medical instability

    b) Disability

    c) Dependency

    d) Institutionalization

    e) Injuries

    f) Falls

    g) Acute illness

    h) Hospitalization

    i) Health care resources utilization

    j) Slow or incomplete recovery from illness and/or hospitalization

    k) High risk of iatrogenesis and side effects from medical interventions

    l) Mortality

2) The prevalence of frailty increases dramatically with age.

3) Frailty is manifested as an impaired ability to cope with challenges in health and reduced ability to regain a stable health status, possibly related to reduced functional reserve. Severity of frailty spans from subclinical to a clinical stage to impending death[7].

4) In aging individuals, the variability in health and functional status is

explained less and less by the effect of clinically evident or even subclinical diseases. Older age is associated with increased vulnerability to multiple diseases with no evident pathogenetic connections. Such global vulnerability is not explained by changes in recognizable risk factors.

5) Frail older persons require intensive and multidimensional continuous care and have high need of community and informal support services. These care needs necessitate a shift in the deployment of heath care resources.

6) Geriatrics is a medical specialty particularly skilled in the care of frail elders.

CONCEPT OF FRAILTY: WHY IS IT COMPELLING?

First, frail individuals are perceived to constitute those older adults at highest risk for a number of adverse events, including disability, dependency, institutionalization, falls, injuries, acute illness, hospitalizations, slow or incomplete recovery from illness and/or hospitalization, and mortality. Additionally, they have compromised ability to tolerate hospitalization or invasive procedures and are at high risk of related complications[7].

Second, frail older adults are thought to be a subset in high need of health care and community and informal support services, as well as long-term care. These special needs were the main basis for the development of comprehensive geriatric assessment and creation of specific geriatric systems for care delivery as

optimal clinical approaches to decreasing preventable adverse outcomes for frail older adults.

Third, the prevalence of frailty is high, with estimates ranging from 10% to 25% of persons aged 65 years and older, with as many as 30% to 45% of those aged 85 years and older identified as frail. Such estimates are based on clinical perceptions of a notable change in vulnerability, health status, and clinical appearance with age in a substantial subset of older adults that is not explained by disease alone.

Fourth, it is thought that the increased risk of adverse outcomes associated with frailty is a result of an increased vulnerability to stressors itself caused by a decreased ability to maintain homeostasis when the individual is stressed. Stressors can be intrinsic, such as infection, or extrinsic, such as change in environment. There is some evidence to suggest that, in addition to those who already appear frail clinically, a subset of older individuals have subclinical frailty, i.e., have increased vulnerability to adverse outcomes in the face of stressors but without the clinical stigmata of frailty or any of its outcomes.

A fifth reason that the concept of frailty has had saliency for geriatricians is the mounting evidence that there is a decrease with age in the ability of disease alone to explain the increased variation in health status, outcomes, or response to therapy. Measures of subclinical organ system changes and physical functional and

cognitive variables, rather than presence or absence of diseases, are the most powerful predictors of longevity and functional outcomes.

Sixth, with increasing age, there is a concurrent, increased susceptibility to multiple chronic diseases that is not explained by “classic” risk factors. This increased susceptibility with no evident pathogenetic connections in risk between the multiple diseases could be related to the progressive collapse of the regulatory network of biological signals aimed at maintaining the homeostatic equilibrium. Seventh, given the discussion above, it would appear that frailty is a condition of impending deterioration in health and functional status that requires immediate attention to prevent disability and other associated outcomes. It requires substantial clinical expertise to both recognize those who are frail and/or vulnerable, and accurately diagnose and effectively intervene to prevent adverse outcomes or frailty itself. Because of the complexity of presentation, attendant vulnerabilities, and multiple health problems likely to be concurrently present, health care in frail older people needs to be skilled, intensive, and continuous to be effective and, therefore, is intrinsically more expensive[7,49].

CONTINUUM OF RESILIENCE - FRAILTY IN OLDER ADULTS

Some clinical reports indicate that there is a subset of older adults with advanced frailty stigmata and significant outcomes, particularly disability or dependency, who have lost reserves and resilience to a point that they have a very high likelihood of dying within 6 to 12 months, and are quite unlikely to respond to therapies, including rehabilitative therapies. These differentiations of vulnerability—with or without the clinical appearance of frailty and its sequelae—are consistent with the idea of a continuum of frailty among older adults as a core component underlying the heterogeneity of health status observed with increasing age. This continuum of frailty incorporates what is thought clinically to be a distinct causal pathway to disability, with frailty being a major etiologic risk factor independent of disease[7,8,13]. Frailty is thought distinguishable from disability (as an outcome) and comorbidity, although there are overlapping co-prevalences[45].

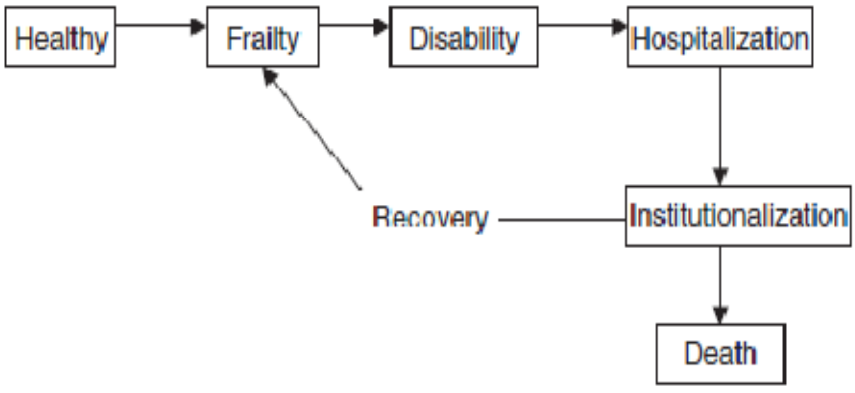


Figure 3 – **CONTINUUM OF RESILIENCE - FRAILTY**

RESILIENCE  **FRAILTY**

Table 1 - **CONTINUUM OF RESILIENCE - FRAILTY**

Robust	**Sub-clinically frail**	**Early Frailty**	**Late Frailty**	**End stage Frailty**
Resilient; recovers readily from stressors.	Appears resilient, but recovers slowly or incompletely from stressors & may manifest adverse consequences.	Clinical appearance of being frail Poor tolerance of stressors; no disability.	Clinical appearance of being frail Poor tolerance of stressors very slow recovery Outcomes: disability due to decreased energy, strength.	Clinical appearance of severe frailty; low LDL, cholesterol, strength; weight loss Outcomes: dependent; high risk of death < 1 yr.

PATHOPHYSIOLOGY OF FRAILTY

Weakness and fatigue are central to almost all definitions of frailty. Sarcopenia (loss of skeletal muscle mass) is likely a key component of these symptoms[7].

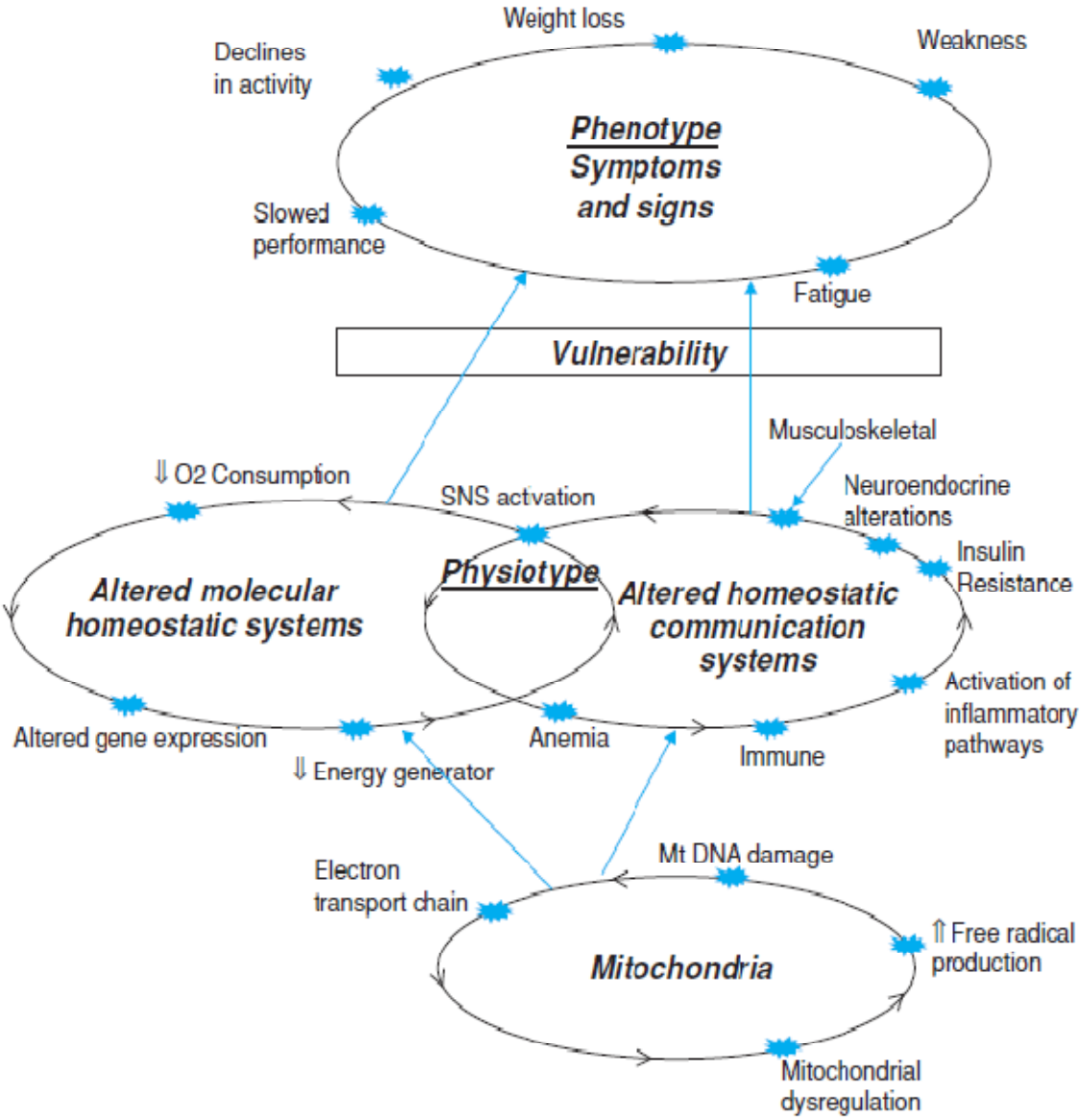


Figure 4 – **PATHOPHYSIOLOGY OF FRAILTY**

Effects of endocrine changes

Changes in the endocrine system play a role in the accelerated decline in muscle mass and strength seen in frail older adults. In women, sex hormone levels decline fairly abruptly with the onset of menopause; in men testosterone levels also decline, but less abruptly[9]. Growth hormone levels also decrease with age. Compared with non-frail older adults, frail older adults have lower levels of the sex hormone dehydroepiandrosterone sulfate (DHEA-s) and insulin-like growth factor-1 (IGF-1), a messenger molecule stimulated by growth hormone. Lower levels of IGF-1 have been shown to be associated with lower strength and decreased mobility in a cohort of community- dwelling older women[14]. Many other hormones and nutrients, including vitamin D, have been shown to preserve muscle strength and hence may play a role in preventing or treating frailty.

Effects of inflammation

Markers of inflammation are also associated with the frailty syndrome. Serum levels of interleukin 6 (IL-6) and C-reactive protein have been found to be elevated in community-dwelling frail older adults[14]. IL-6 is strongly associated with adverse physiologic effects such as sarcopenia, weight loss, and an increased susceptibility to infection. In addition, IL-6 may contribute to anemia by directly inhibiting production of erythropoietin or by interfering with normal iron

metabolism. In a cohort of community-dwelling older adults, subclinical normocytic anemia was observed in those who were frail, and an inverse correlation was found between serum IL-6 and hemoglobin levels. This chronic inflammatory state likely also contributes to other hematologic effects such as activation of the clotting cascade[39]. Indeed, frail older adults have been found to have significantly elevated levels of factor VIII, fibrinogen, and D-dimer.

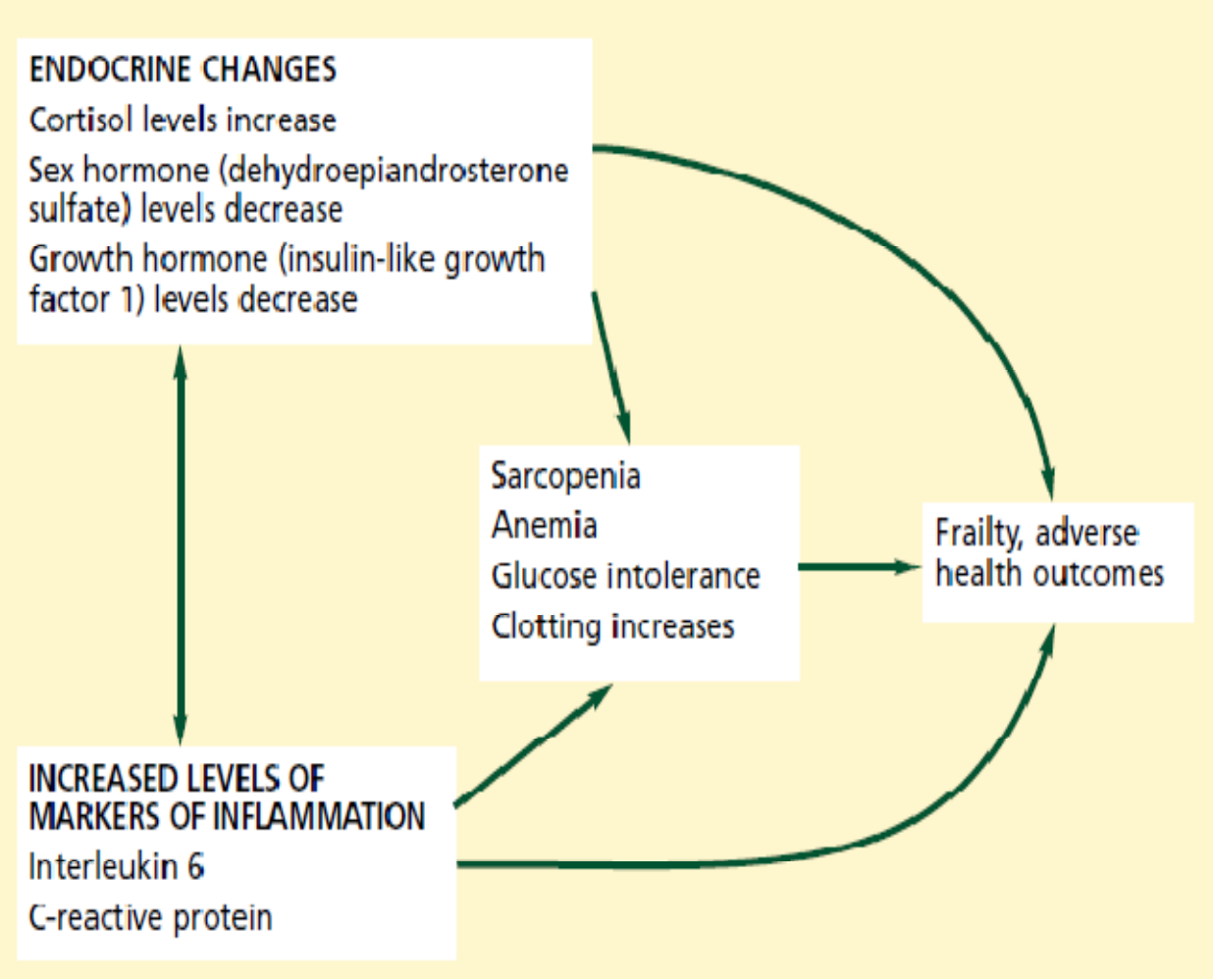


Figure 5 – **ENDOCRINE CHANGES & FRAILTY**

Interaction of systemic changes is likely

The physiologic findings and other features that characterize frailty are not likely to be the result of changes in a single system, but rather of the interaction of several systems resulting in a global process[25]. For example, the combination of low IGF-1 and high IL-6 levels in a cohort of community- dwelling older women conferred a high risk for progressive disability and death that was greater than the effect of either of these two factors alone, suggesting an additive effect. Similarly, Roubenoff showed that increased cellular production of tumor necrosis factor alpha and IL-6 and decreased cellular production of IGF-1 were associated with increased death rates over 4 years in a cohort of community-dwelling older adults. These findings persisted after adjusting for potential confounders such as chronic disease.

Factors influencing frailty[8]

- Disease
    - Diabetes mellitus
    - Chronic obstructive pulmonary disease
    - Anemia
    - Polymyalgia rheumatica
    - Endocrine disorders

- Decline in executive function
- Decreased food intake
    - Social factors
    - Congestive heart failure
    - Decline in taste and smell
    - Altered fundal compliance
    - Enhanced release of cholecystokinin
    - Increased leptin
    - Cytokines
- Pain
- Excess muscle loss (Sarcopenia)
    - Lack of physical activity
    - Poor nutritional intake
    - Decline in anabolic hormones
    - Increased cytokines
    - Reduced nerve motor units
    - Peripheral vascular disease
    - Age

Disease

Numerous disease processes can directly or indirectly result in frailty. Many diseases produce excess of cytokines that can lead to decreased muscle mass, food intake and cognitive function. Diseases also lead to a decline in levels of the anabolic hormone, testosterone.

Congestive heart failure (CHF) is a condition that is classically associated with frailty. Persons with CHF have a marked decline in their VO_2 max, leading to an inability to perform endurance tasks. Left-sided heart failure leads to intestinal wall edema.

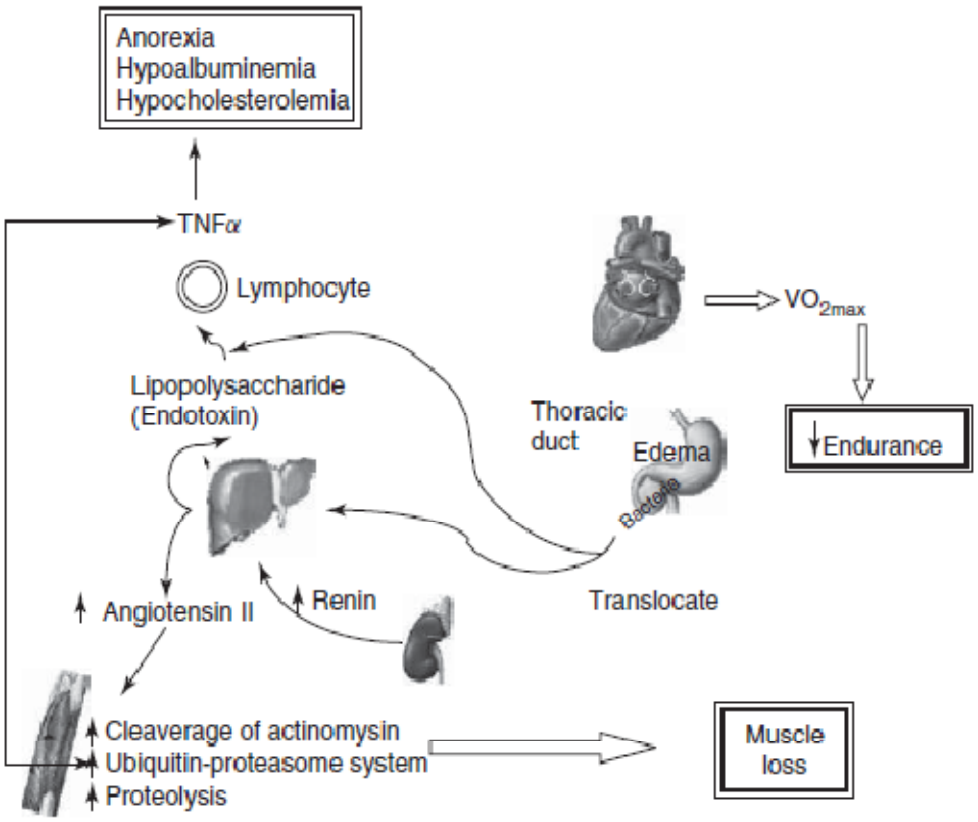


Figure 6 **– CCF & FRAILTY**

This results in bacterial translocation into the lymphatic and systemic circulation. The bacterial endotoxins (LPS) result in the activation of the immune system and release of cytokines, such as TNF α[18]. This results in anorexia, loss of muscle mass, weight loss, hypoalbuminemia, and hypocholesterolemia. In CHF, the best predictors of poor outcome are weight loss and hypocholesterolemia. Activation of the angiotensin II system that leads to cleaving of actomyosin and subsequent clearance of muscle protein by the ubiquitin-proteasome system may also play a role. Angiotensin-converting enzyme inhibitors reverse weight loss and frailty in some persons with CHF.

Persons with chronic obstructive pulmonary disease have a decrease in endurance, weight loss due to poor food intake[68], and increased resting metabolic rate and thermic energy of eating. They lose muscle because of low testosterone levels and increased circulating cytokine levels.

Diabetes mellitus is classically associated with an increase in frailty, injurious falls, disability and premature death[20,42]. Again, the causes are multifactorial and include low testosterone, increased angiotensin II, increased cytokines, peripheral neuropathy, reduced executive function and accelerated atherosclerosis[72].

Persons with anemia have reduced endurance[46], decreased muscle strength, orthostasis, increased falls, increased frailty, decreased mobility, increased

disability and increased mortality. Both erythropoietin and darbopoetin-α can reverse the anemia and many of these changes. The use of these agents has led to a marked increase in the quality of life of patients with chronic kidney failure, anemia of chronic disease, and myelofibrosis.

Polymalgia rheumatica is a condition associated with painful muscles and proximal myopathy. It is confirmed by an elevated erythrocyte sedimentation rate. Treatment of this condition with corticosteroids can reverse the frailty it produces. Unfortunately, this totally reversible condition is often misdiagnosed by clinicians.

Endocrine disorders, such as Addison's disease, hyperthyroidism and hypothyroidism can have insidious onset in elderly individuals. When this occurs, they are the classical causes of frailty.

Pain

Joint pain (arthritides) is classically associated with immobility. Immobility, over a period of time, leads to loss of muscle mass and power and to a decline in endurance, the hallmarks of frailty. Pain can further induce frailty secondary to aggravating depression in elders.

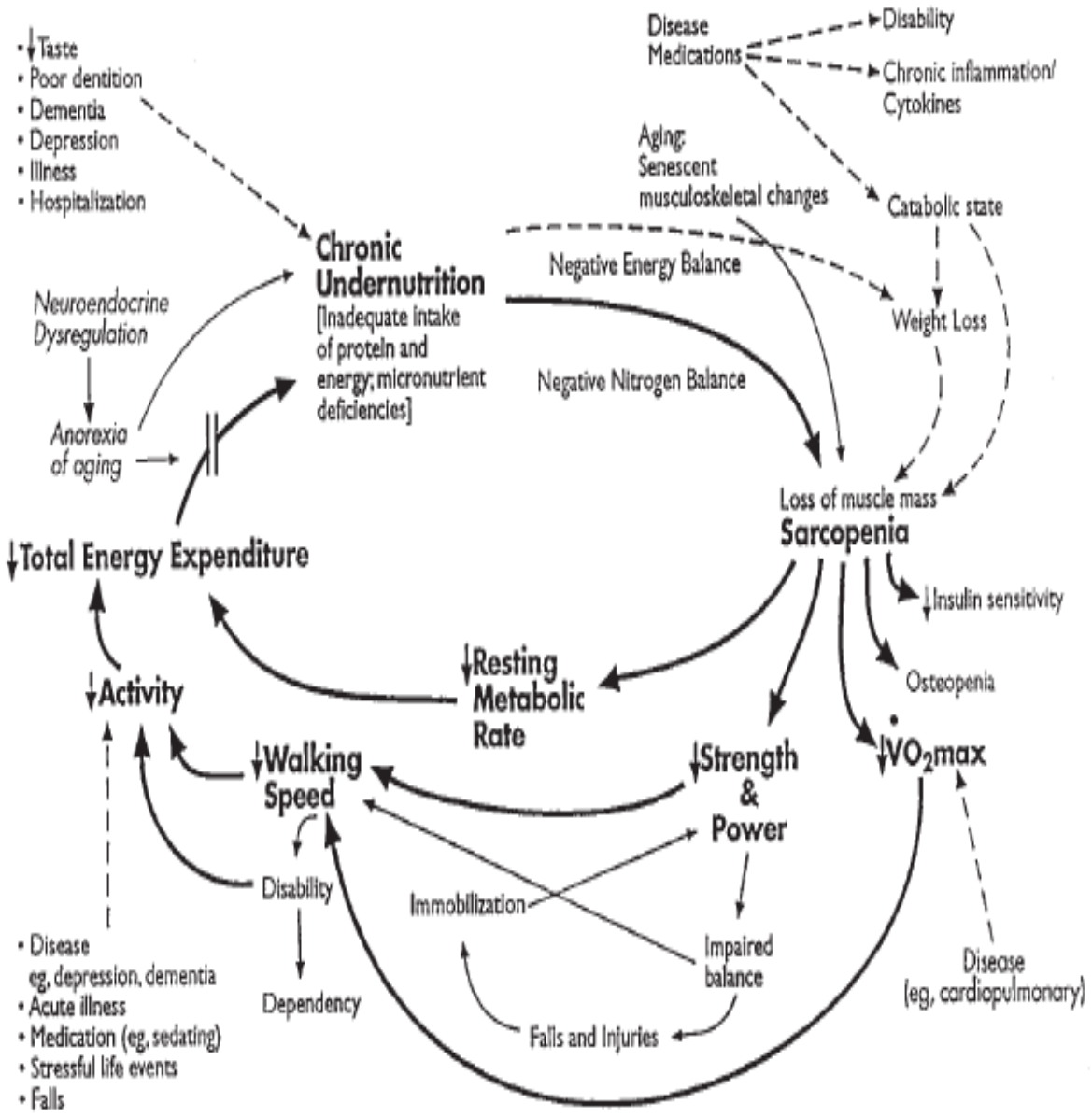


Figure 7 - **CYCLE OF FRAILTY**

Integrating causal relationships between signs and symptoms[8].

Sarcopenia

Sarcopenia (from the Greek meaning "poverty of flesh") is the excessive loss of muscle mass that occurs in older persons. It is usually defined as a greater than two standard deviations amount of lean tissue loss compared to that of younger persons[23,37]. It occurs in 13–24% of persons aged 60–70 years and in about 50% over 80 years of age[23,34,35]. The best measure of sarcopenia is based on the appendicular skeletal mass in kilograms as measured by DEXA, divided by the height in meters squared. It can also be calculated using magnetic resonance imaging (MRI), computed tomography (CT), or bioelectrical impedance. DEXA and MRI measures are highly correlated. Sarcopenia is strongly correlated with disability[37]. Most sarcopenic individuals have lost fat as well. However, a subset of individuals remain fat while losing muscle mass. These individuals have been characterized as the "sarcopenic obese" or the "fat frail"[27]. Longitudinally, those with obese sarcopenia have been found to be the most likely to develop future disability and mortality[37]. Myosteatosis – the infiltration of fat into muscle – appears to be a separate condition related to insulin resistance. Mitochondrial failure or elevated circulating triglycerides lead to accumulation of triglycerides within the cell. This alters the function of the insulin receptor substrate and, therefore, the GLUT transporter, leading to insulin resistance. The development of sarcopenia and its effect on frailty have been characterized in the worm

Caenorhabditis elegans. In *C. elegans*, muscle deterioration (sarcopenia) with aging leads to a decline in body movement. The muscle deterioration also correlates with behavior deficits (a frailty equivalent). These changes rarely correlated with a decreased life span. Mutations in daf-2 (the worm's IGF-1) delay these changes.

Sarcopenia of aging is not explained entirely on the basis of age-associated reduced physical activity. Progressive neuromuscular changes and diminishing anabolic hormone levels are thought to contribute to the pathogenesis of sarcopenia. Decline in muscle mass indicates a decline in muscle protein content. Recent studies demonstrated an age-related decline in synthesis rate of mixed muscle proteins, myosin heavy chain and mitochondrial protein. Reductions in myosin heavy chain and mitochondrial protein synthesis rates have been correlated with age-associated decrements in muscle strength and aerobic exercise tolerance, respectively. These changes have been reported as early as 50 years of age and are related to the decline in insulin-like growth factor (IGF-1), testosterone and dehydroepiandrosterone sulfate (DHEA-s). The declining ability to remodel these important muscle proteins may therefore play a role in the development of muscle wasting, metabolic abnormalities and impaired physical functioning seen in old age[11,12,26].

There is evidence that sarcopenia originates at birth. In the Hertfordshire cohort study, it has been shown that grip strength correlates with birth weight. Genetic studies have shown that persons with a single I or double I allele for angiotensin-converting enzyme appear to be able to generate more power when exercising regularly than those with D allele.

Epidemiological studies have suggested that the best predictors of muscle mass and strength in older persons are age, energy intake, physical activity, IGF-1, testosterone, and cytokines[21,30,37]. Testosterone levels decline at the rate of 1% per year from the age of 30 years in men and rapidly between 20 and 40 years in women[33,66]. Testosterone inhibits the movement of pluripotential stem cells into the fat cell lineage and stimulates the muscle cell lineage to result in the production of satellite cells. Satellite cells are essential for the repair of skeletal muscle[22]. Testosterone also stimulates muscle protein synthesis and inhibits the ubiquitin-proteasome pathway, resulting in a decrease in muscle protein turnover. Testosterone replacement, even in non-hypogonadal males, increases muscle mass[25].

Pharmacological doses of testosterone or testosterone replacement in hypogonadal males lead to an increase in muscle strength and muscle power. These changes have now been shown to lead to functional improvement. However, there is a small amount of evidence that testosterone has similar effects in older women.

A number of selective androgen receptor molecules (SARMs) are being developed, in an attempt to find androgenic compounds that have a specific effect on muscle but are less likely to produce side effects.

Steroids	***Nonsteroidal***
-Nandrolone	-2-Quinoline
-Oxymethalone	-Coumarin
-Oxandrolone	-Phthalimide
	-Acetothiolutamide
	-Bicalcutamide

Another anabolic hormone, Growth Hormone, increases muscle mass but not strength in older persons. The effect of growth hormone is predominantly on type-II muscle fibers.

Ghrelin, a growth hormone secretagogue produced in the fundus of the stomach, also appears to increase muscle mass.

Insulin growth factor (IGF) is produced in three alternative forms in muscle. One of these forms, a mechanogrowth factor (MGF) is produced in response to mechanical overload. The ability of MGF to be produced in response to mechanical overload declines with aging. Resistance exercise increases MGF in human quadriceps[24], and this increase is greater when growth hormone is also given. IGF enhances satellite cell production.

Myostatin D inhibits muscle growth. A double deletion of myostatin D in mice leads to muscle hypertrophy, a veritable “mighty mouse”. Motor unit functioning is essential for the maintenance of muscle function. Motor unit firing rate is significantly decreased in the old-old, that is, those over 80 years of age.

Ciliary neurotrophic factor (CNTF) levels decline with age and this decline correlates with the decrease in muscle strength with aging. Administration of CNTF leads to twofold increase in soleus muscle size.

Cytokines are soluble peptide messengers that are synthesized by white cells, neuronal cells and adipocytes. Excess of tumor necrosis factor-α and interleukin-6 leads to loss of muscle strength. High levels of C-reactive protein and interleukin-6 are associated with a decrease in handgrip strength and in physical performance.

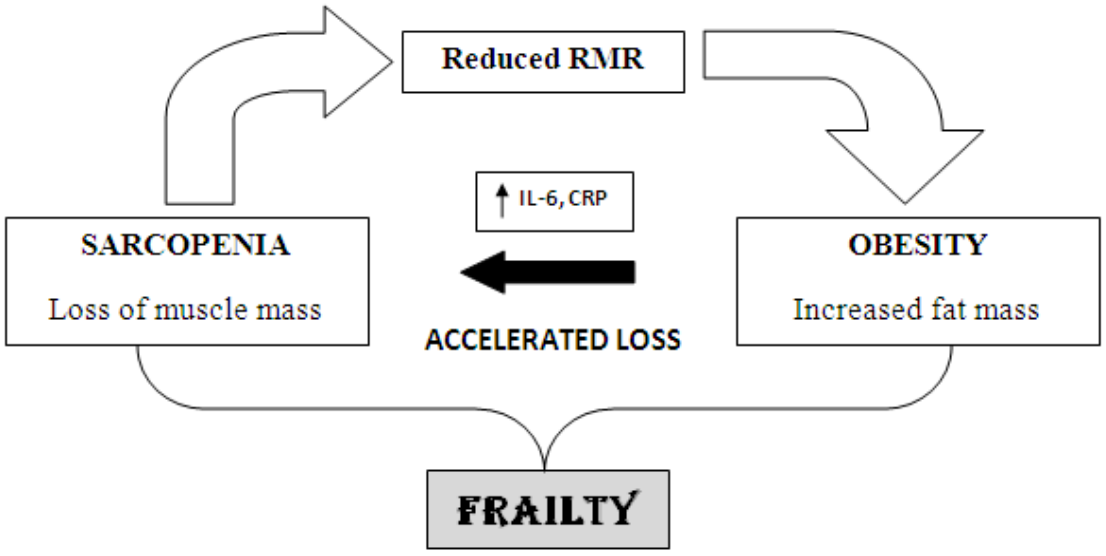


Figure 8 **– FRAILTY & SARCOPENIC OBESITY**

Elevated homocysteine levels and peripheral vascular disease lead to reduced blood flow to muscles which causes muscle atrophy and decreased function. Creatine is an essential amino acid for muscle. Creatine, together with exercise, may improve muscle performance in older persons. Finally, the development of sarcopenia depends on an imbalance in the normal everyday renewal cycle of muscle. There is either an excess of atrophy and apoptosis or a diminution of hypertrophy and satellite cell production.

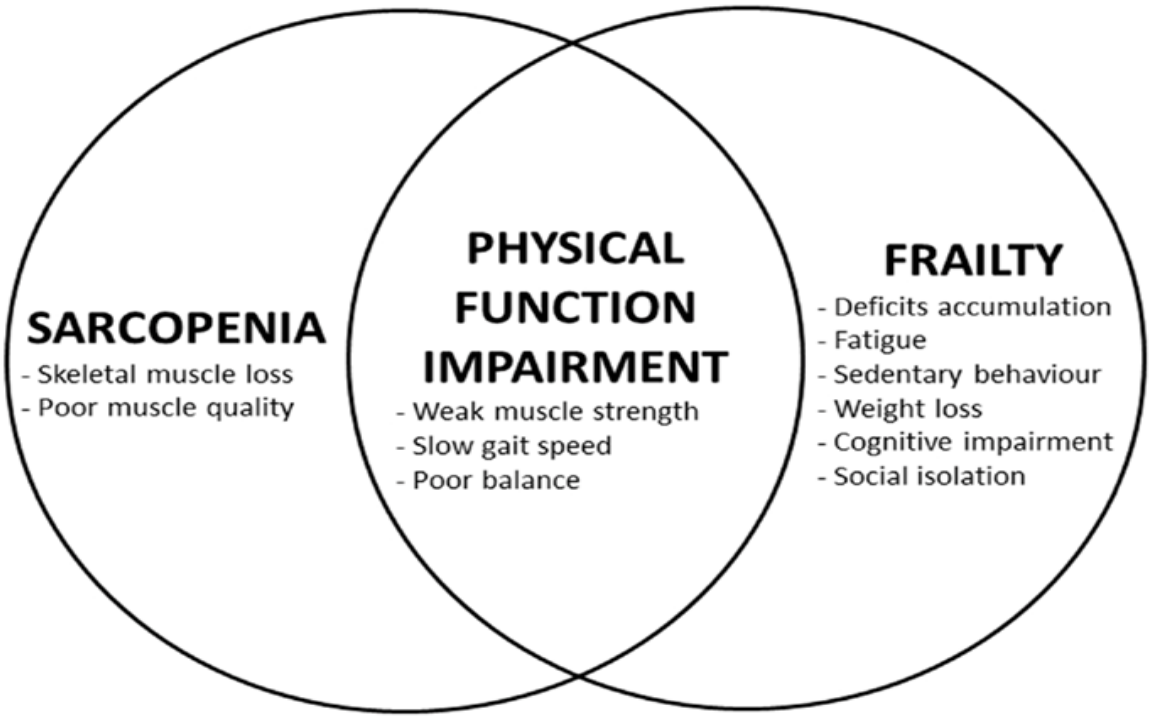


Figure 9 – **VENN DIAGRAM DEPICTING RELATIONSHIP BETWEEN FRAILTY & SARCOPENIA**

Decreased Food Intake

Older persons develop anorexia of aging physiologically that is associated with a loss of weight. Social causes, such as isolation and dysphoria, and the decline in smell and increase in taste threshold are other causes. Recently, there have been a number of studies that demonstrated that decreased compliance and adaptive relaxation of the stomach results in a more rapid antral filling and early satiety. Cholecystokinin produced by the duodenum in response to a fatty meal is another cause of anorexia in elders. High circulating cytokine levels in older persons have been associated with anorexia. With advancing age, males have a greater decrease in both absolute and relative amounts of food intake. This appears to be due to the fall in testosterone level, which results in an increase in leptin level and, therefore, a greater anorexia[68].

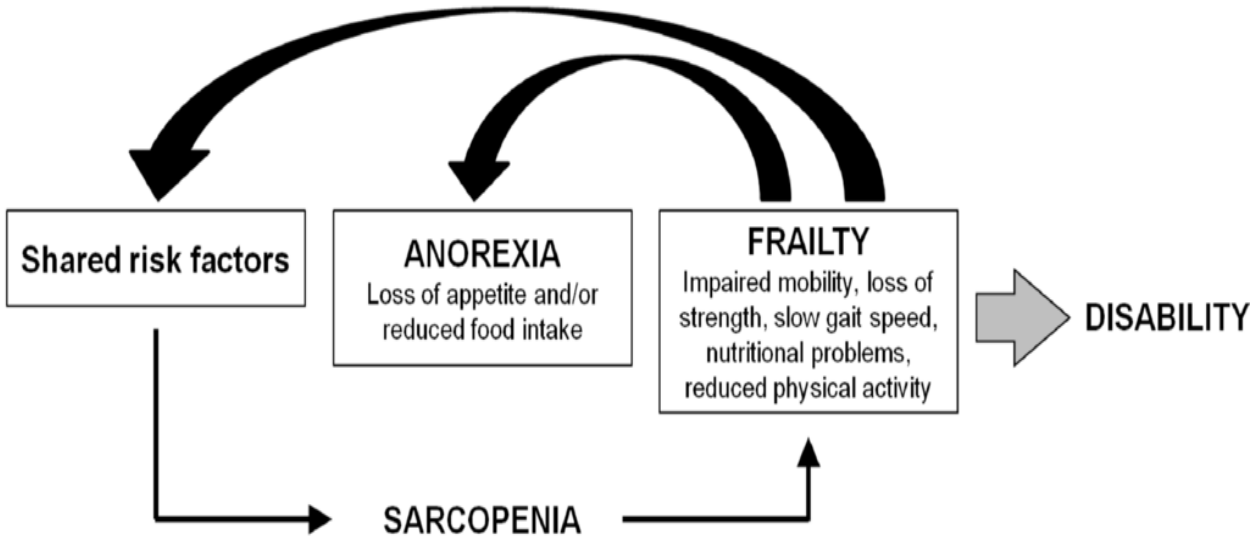


Figure 10 **– ANOREXIA & FRAILTY**

SYNDROMIC NATURE OF FRAILTY

There are inputs at multiple levels including (1) biologic, (2) altered physiological functions in homeostatic systems and altered communications systems, and then (3) a clinical presentation that appears to be the outcome of these multiple changes and constitutes a constellation of presentations that are interrelated in themselves and likely involved in a vicious cycle of dysregulated energetics. The aggregate impact of dysfunction at multiple levels is thought to result in compromised ability of the organism to maintain homeostasis and the vulnerability to stressors manifested by frail older adults[7,10].

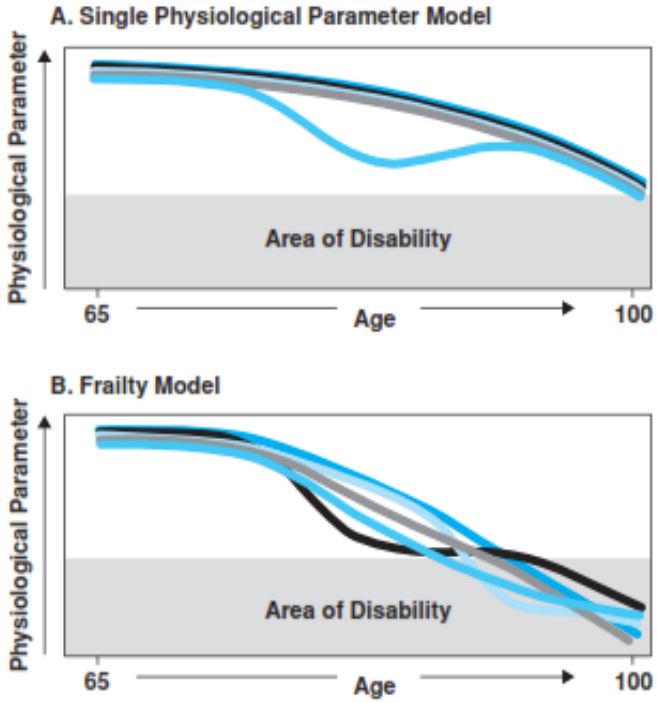


Figure 11 - **SYNDROMIC NATURE OF FRAILTY**

The clinical phenotype of frailty is based on proposed interrelationship of decline in physical activity level, performance, energy, strength and weight loss. Sarcopenia contributing to altered energy production and utilization is a well established fact. With loss of muscle mass and decreased muscle function, there is a decline in muscle strength and exercise tolerance. The latter can be validly represented by the concept of "fatigue" or "exhaustion." Although it directly relates to the amount of physical work the individual can produce, "fatigue" or "exhaustion" may also directly result from altered cellular production or consumption of energy. Further, there is evidence that declines in strength and exercise tolerance predict both slower walking speed and further decreases in performance level. In a subset of elders, who maybe frail (although that is not yet demonstrated), there is a mismatch between inadequately low food intake and inadequately high energy expenditure through physical activity (even at low levels), resulting in further loss of muscle and, in cases extremely severe cases, weight loss. These interconnections support the concept of a "cycle" of frailty. There is now evidence that this cycle has a natural history of chronic progression that often begins with declines in strength and/or walking speed, which then predicts declines in physical activity[15,41]. However, when strength, walking speed, and physical activity are all impaired, then the system rapidly progresses toward frailty[7,40].

A number of physiologic systems at abnormal levels have been shown to be associated with the frailty phenotype above[16,17,32]. These include sarcopenia and higher fat deposits in muscle, low testosterone, insulin, DHEA-s and IGF-1[36,63], blunted diurnal variation and higher levels of cortisol, insulin, elevated pro-inflammatory markers (i.e., IL-6 and C-reactive protein [CRP]), elevated markers of blood clotting, anemia[46], low micronutrient levels (especially total carotenoids, beta carotene and lutein/zeaxanthin), decreased immune function[38] (with decreased T-cell proliferation and altered cytokine production), and decreased heart rate variability. Further, the severity of abnormality within each system and, particularly, the number of systems at abnormal levels are associated with the presence and severity of frailty. Frail older women are more likely to have two or more micronutrient deficiencies and low daily energy intake of 21 kcal/kg or less, along with low intake of protein, vitamins D, E, C, and folate. Thus, circulating antioxidants are low in those who are frail compared to non-frail[18,28,29]. New evidence indicates that the risk of frailty is highly associated with multiple systems at abnormal levels, significantly more than any one system described above. The multiplicity of systems at abnormal levels is the hallmark of frailty. In spite of overwhelming evidence that age and frailty affect multiple physiological parameters in parallel, most research on biomarkers of aging is based on single measures.

STANDARDIZED APPROACHES TO ASCERTAIN FRAILTY

Several approaches have been developed to identify those who are frail. One, developed by Rockwood and colleagues[43,48,71], described above, creates a summary measure of deficit accumulation (termed "frailty index (FI)") across many different types of health conditions at many levels: functional, clinical, and physiological. It was designed to quantifying the theorized impact of aggregate disease and illness burden. The investigators have shown that increasing numbers of conditions present are associated with a stepwise increase in mortality risk. Inferentially, they theorize that the aggregate physiological effect of these multiple conditions is "frailty." This approach has the two main disadvantages: the number of parameters to be collected makes it unsuitable for clinical utilization and, second, it does not offer a unifying theory as to etiology that might guide prevention and treatment.

A second approach posits, consistent with discussion in the prior section, that there is a distinct pathophysiology to frailty with a syndromic clinical presentation. Several groups have proposed related approaches, building on the observation of characteristic signs and symptoms of people who are "frail." In 1999, Paw et al. posited that inactivity and malnutrition were two major determinants of frailty that jointly provide strong prediction of the adverse outcomes of frailty. In the Zutphen Elderly Study, they found the combination of

inactivity (less than 210 mins of physical activity per week) and weight loss (more than 4 kg over 5 years) identified 6% of this cohort of older men as “frail,” and predicted slow walking speed, and greater disability and mortality. By necessity, these authors used weight loss over 5 years, but identified this as a limitation to sensitivity and suggested use of weight loss over the last year instead. Overall, the authors claim that this approach offers a simple, inexpensive, and effective screening for identifying a frail population.

In 1998, Fried and Walston[6,44] proposed that there were a few major presenting symptoms and signs of frailty, and that these were interrelated in a vicious cycle, or feed-forward loop, resulting from dysregulated energetics with declines in strength, energy, walking speed, physical activity, and weight loss (over 1 year), all interrelated and presenting cardinal manifestations of a clinical syndrome of physical frailty.

This proposal was subsequently operationalized by defining the frail as those with a critical mass of clinical manifestations, i.e., three or more. This definition has been validated (face, criterion, construct, predictive) in more than five population-based studies as identifying those at high risk of disability, falls, hospitalization, hip fracture, and mortality. Further, this frailty phenotype has been shown to have characteristics of a medical syndrome, in which the multiplicity of signs and symptoms present identifies those who are frail more than any one or

two. Risk of adverse outcomes is more strongly associated with the constellation of presentations than with any one or two and no specific cluster of criteria carry distinguishable risk. This approach to characterizing frail older adults is based on the theory of a discrete syndrome with specific definable causes, both biological and environmental. By this definition of frailty, prevalence is 7% overall in community-dwelling men and women aged 65 years and older, and increases with increasing age from 3% in those 65 to 74 years up to 25% in those 85 years and older. There is a twofold higher prevalence in African-American older adults, compared to whites, at each age group 65 years and older. Using this definition, there is now evidence as to the natural history of frailty, indicating it is a dynamic but generally chronic, progressive condition, with 43% transitioning to states of greater frailty over 18 months, while 23% transitioned to states of lesser frailty, and almost no one transition from frail to being non-frail. Further, initial presentations of frailty are most likely to be decreased strength or slow walking speed, which then predict development of additional manifestations, consistent with the hypothesis of a cycle of frailty. Those with one or two manifestations are at twofold higher risk of progressing to three, four, or five over 3 years, thus suggesting they are pre-frail. There is now strong evidence for the association of this clinical phenotype with dysregulation in number of physiologic systems. Thus, with this approach, frailty can be thought about in terms of a core phenotype

manifesting a syndrome, with definable outcomes and recognized etiology. Ongoing research aims to define the physiological alterations and the ultimate biological causes of frailty.

As stated by Bergman[62], the underlying assumption of an operational definition of a syndrome, based on symptoms, is that domains used for the diagnosis do not represent all possible manifestations of the syndrome; rather, they constitute the important domains that can be easily and reliably measured and together maximize specificity of the diagnosis. Because many components of the pathological process are associated with each other, it is not necessary to require the presence of all of them to make the diagnosis. Consistent with this, these authors suggest that the phenotype described above, with distinct, standardizable measures and criteria for definition, built on biologic theory, validated with diagnostic criteria that are strongly age-related, lends itself for use in screening, diagnosis, and as a basis for prevention and treatment of frailty. A disadvantage of this particular definition, however, is that assessment requires approximately 10 to 15 minutes: to weigh a patient, measure grip strength and walking speed, and to ask two questions regarding “exhaustion” and a physical activity questionnaire. Studenski and others advocate that measurements of walking speed and possibly strength should be considered geriatric “vital signs” and assessed regularly in clinical settings. If this is implemented generally in clinical practice, then the time-

consuming part of this assessment is determining physical activity level; methodological work is needed to develop a more parsimonious approach to screening physical activity than current questionnaires offer.

An alternative approach has been proposed for clinical characterization of patients as frail and using clinical judgment particularly to measure change over time clinically and/or in response to treatment. A global impression of change in frailty has been developed by Studenski and colleagues to represent the clinician's perspective on clinically meaningful change resulting from interventions on physical frailty, e.g., nutrition, exercise, medications, and multifactorial approaches. This measure records clinician judgment regarding the domains of intrinsic frailty (strength, balance, nutrition, stamina, physical activity, neuromotor function, and mobility) plus appearance, medical complexity, perceived health, healthcare utilization, and outcomes of frailty (physical disability in basic, instrumental, and advanced functions; emotional status; and social status). Its goal is to create a reference point for defining the magnitude of change in simple objective measures in order to eventually measure effects of interventions to prevent or treat frailty, integrating clinical meaning with traditional measurement properties[7].

REPORTED COMPONENTS OF THE FRAILTY SYNDROME

The components of frailty according to various references are tabulated[31].

REFERENCE	MOBILITY	STRENGTH	BALANCE	MOTOR PROCESSING	COGNITION	NUTRITION	ENDURANCE	PHYSICAL ACTIVITY
Winograd CH et al.	X				X	X		X
Ory MG et al.	X	X	X		X		X	
Pendergast DR et al.		X	X	X			X	
Rockwood K et al.					X			X
Tinetti ME et al.	X	X						
Gill TM et al.	X		X					
Campbell AJ et al.		X	X	X	X	X	X	
Dayhoff NE et al.		X	X					
Strawbridge WJ et al.	X				X	X		
Chin APMJ et al.						X		X
Vellas B et al.		X				X	X	X
Brown M et al.	X	X	X	X				
Fried LP et al.	X	X				X	X	X
Saliba D et al.	X							

Table 2 - **FRAILTY COMPONENTS AS PER VARIOUS REFERENCES**

OBJECTIVE DEFINITION OF FRAILTY:

FRIED'S CRITERIA:

A popular approach to the assessment of geriatric frailty encompasses the assessment of five dimensions that are hypothesized to reflect systems whose impaired regulation underlies the syndrome[6]. These five dimensions are:

- Weight loss
- Exhaustion
- Weakness
- Walking speed
- Physical activity

CUT-OFFS USED TO DEFINE FRAILTY:

1) Weight loss:

In the past year have you lost more than 10 lb (5% of previous year's body weight) unintentionally? (not due to dieting or exercise). If yes, subject is frail for weight loss criterion.

2) Exhaustion:

Using the Centre for Epidemiological Study – Depression scale (CES-D), the following two statements are read.

1) I felt everything I did was an effort.

2) I could not get going.

The question is asked. How often in the last week did you feel this way?

0 = rarely or none of the time (<1 day)

1= some or a little of a time (1-2 days)

2 = moderate amount of time (3-4 days)

3 = most of the time

Subjects answering '2' or '3' to either of the question is categorized as frail by exhaustion criterion.

3) **Physical activity:**

It is measured by the short version of minnesota leisure time physical activity questionnaire. This is a commonly used, interviewer-administered questionnaire that assesses daily physical activity accumulated during leisure time and household activities over the past 1 week. It takes about 20 minutes to complete the questionnaire. Physical activity was calculated based on the number of minutes spent in each specific activity per week. Physical activity energy expenditure (in kcal/week) was used for data analysis.

Male: Those with < **383 Kcal/week** of physical activity are considered to be frail according to this criterion.

Female: Those with < **270 Kcal/week** of physical activity are considered to be frail according to this criterion.

4) Walking speed

Stratified by gender and height (gender specific cut off at median height).

	Cut-off for time to walk 15 ft - criterion for frailty
Male	
Height ≤ 173 cm	≥ 7 s
Height > 173 cm	≥ 6 s
Female	
Height ≤ 159 cm	≥ 7 s
Height > 159 cm	≥ 6 s

5) Grip strength:

It will be measured in the dominant hand using a Hand Dynamometer. Three attempts at maximal squeeze will be calculated. Average value will be stratified by gender and body mass index (BMI) quartiles.

	Cut-off for grip strength (kg) - criterion for frailty
Male	
BMI ≤ 24	≤ 29
BMI 24.1-26	≤ 30
BMI 26.1-28	≤ 30
BMI > 28	≤ 32
Female	
BMI ≤ 23	≤ 17
BMI 23.1-26	≤ 17.3
BMI 26.1-29	≤ 18
BMI > 29	≤ 21

INFERENCE:

A subject is frail if he/she has ≥ 3 components; Intermediate subjects have 1 or 2 components; and subjects with 0 positive frailty factors are considered not frail.

BIOMARKERS OF FRAILTY

One hallmark of frailty is the dysregulation of homeostatic or communications systems, at both the molecular and physiological level. As mentioned previously, declines in hormones important in muscle mass maintenance such as IGF-1 and DHEA-s, and increases in afternoon cortisol levels and in inflammatory and clotting markers, point toward the immune and neuroendocrine systems as likely candidates as the physiological source of this dysregulation[52].

Aging and frailty are associated development of a mild pro-inflammatory state, indicated by increased levels of pro-inflammatory markers. It has been demonstrated that, among non-disabled older persons, those in the highest IL-6 tertile are at high risk of developing disability over a 4-year follow-up. Older persons with elevated IL-6 and high CRP had higher mortality and there is some evidence that a short-term increase in IL-6 is a strong, independent predictor of mortality. Additionally, some studies suggest that the causal link between inflammation and disability is accelerated sarcopenia. In accordance with this hypothesis, there is increasing evidence that inflammation is involved in the pathogenesis of age-related muscle wasting, perhaps by the up-regulation of the NF-κB activation of the ubiquitin proteasome pathway. Adiposity appears to play an important role in the inflammatory process, and, possibly, the onset of

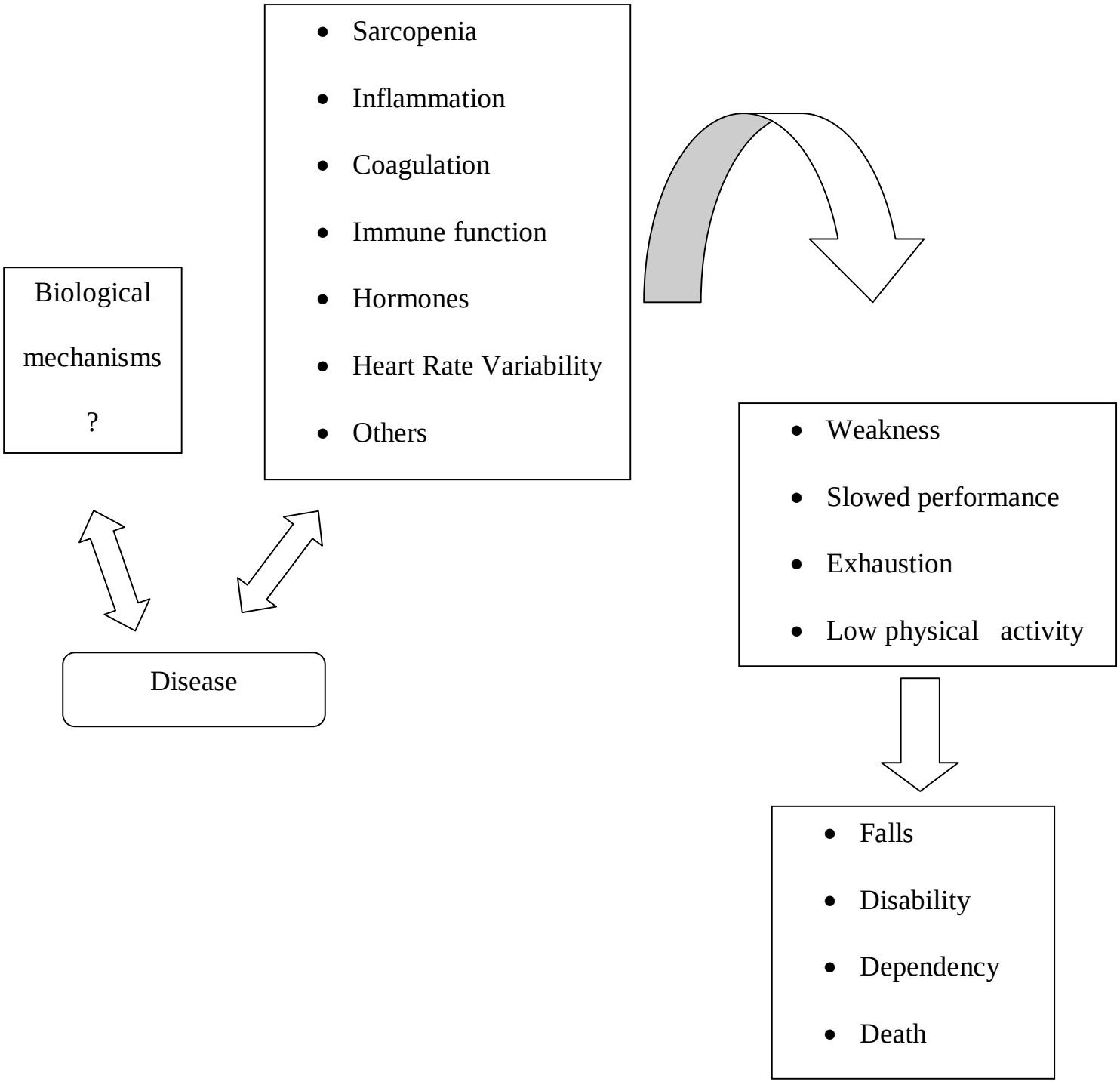
sarcopenia. Studies have suggested that inflammatory cytokines produced by adipose tissue, especially visceral fat, accelerate muscle catabolism and may contribute to the vicious cycle that initiates and sustains sarcopenic obesity and may lead to frailty in older persons. There is cogent evidence of a connection between inflammation and frailty, but whether the link between these two conditions is completely explained by the effect of inflammation on sarcopenia is unclear. Inflammatory states also affect energy availability, hematologic, and hormonal status.

A recent but robust literature suggests that inadequate intake of antioxidant and anti-inflammatory nutrients (in particular selenium, vitamin E, cholecalciferol, carotenoids, and polyunsaturated fatty acids (PUFAs) contribute to sarcopenia and decline in physical function in older persons. In the InCHIANTI baseline evaluation, plasma alpha-tocopherol, was significantly correlated with knee extensor strength and lower extremity performance. Intake of vitamin C and beta-carotene were significantly correlated with knee extensor strength, and vitamin C was significantly associated with lower extremity performance. In addition, low selenium level was independently associated with poor muscle strength and higher mortality. In the WHAS, low selenium level was a risk factor for mortality and future increase in inflammatory markers, and in conjunction with low vitamins B-6

and B-12, was an independent risk factor for mortality. Low alpha-tocopherol was an independent correlate of frailty and poor cognitive function. Both in WHAS and InCHIANTI, low carotenoids was an independent risk factor for accelerated decline of muscle strength and incident disability. Thus, deficient intake of multiple nutrients is an independent correlate of frailty, even after adjusting for total energy intake.

Sirtuins are a class of proteins that possess NAD dependent deacetylase activity. They have been implicated in influencing a wide range of cellular processes like ageing, transcription, apoptosis, inflammation and energy homeostasis. Sirtuins can also control circadian clocks and mitochondrial biogenesis. Preliminary studies with resveratrol, a possible SIRT 1 activator, have led some scientists to speculate that resveratrol may extend lifespan.

Figure 12 - **MODEL PATHWAY OF FRAILTY**



DEHYDROEPIANDROSTERONE

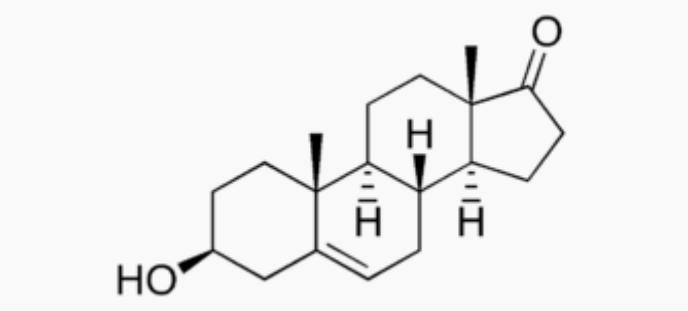


Figure 13 **– STRUCTURE OF DHEA**

Dehydroepiandrosterone (**DHEA**) more correctly didehydroepiandrosterone; also known as androstenolone is an important endogenous steroid hormone. Its chemical formula is $C_{19}H_{28}O_2$ and molecular mass is 288.424 g/mol. It is the most abundant circulating steroid in humans, in whom it is produced in the adrenal glands, the gonads, and the brain, where it functions predominantly as a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids. However, DHEA also has a variety of potential biological effects in its own right, binding to an array of nuclear and cell surface receptors, and acting as a neurosteroid.

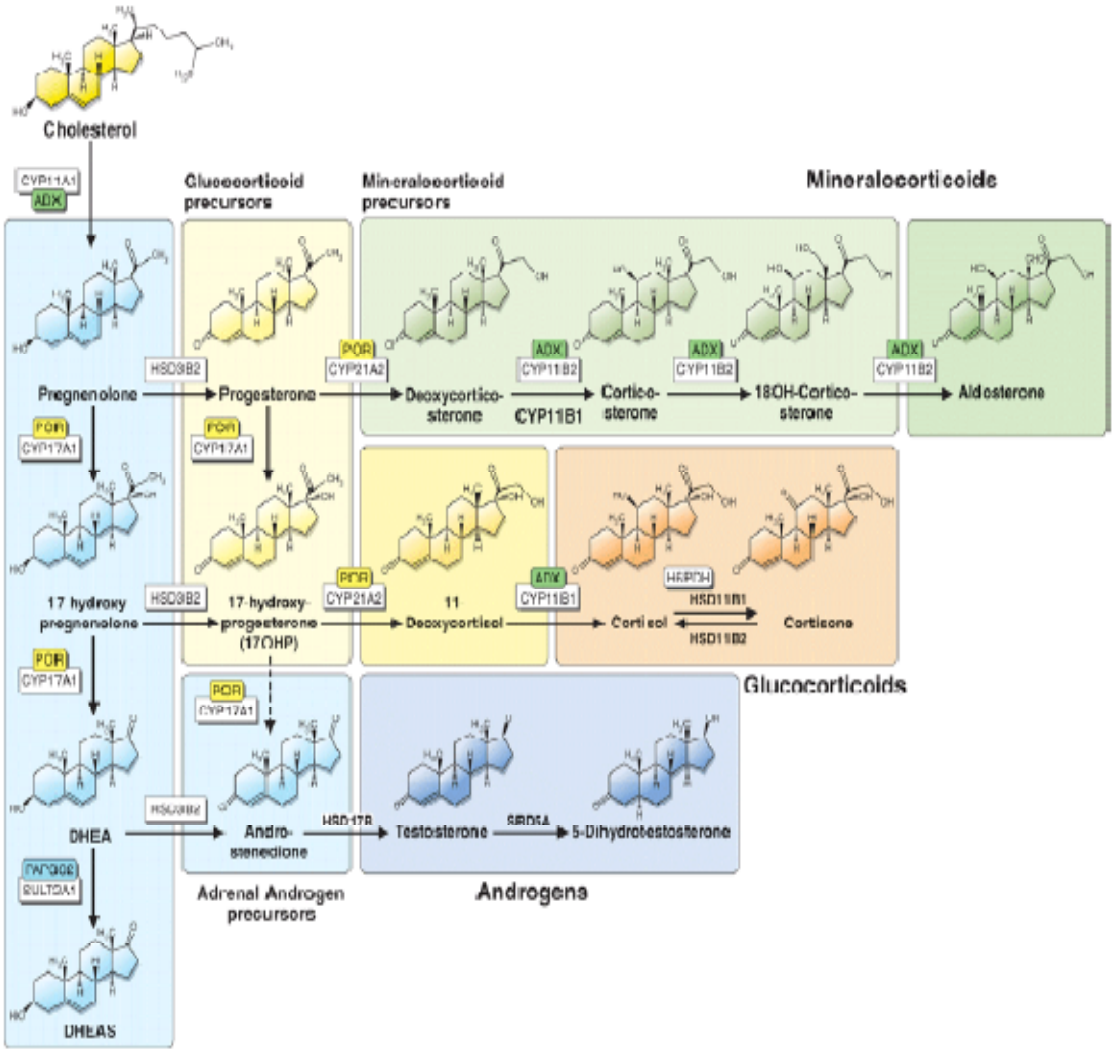
Dehydroepiandrosterone (DHEA) and its sulphate ester (DHEA-s) are prominent adrenal steroid hormones in humans. DHEA influences peripheral tissues either indirectly via a conversion to androgens, estrogens or both, or directly as a steroid hormone. DHEA shows a characteristic secretion pattern

throughout life, with serum levels declining with increasing age. Serum DHEA levels peak in young adults and gradually decline throughout life, so that individuals 70– 80 years old have circulating DHEA levels that are 10–20% of their young adult levels[53]. This age-associated decrease has been termed ‘adrenopause’ and differs from other adrenocortical hormones, which do not demonstrate clear age-related changes[36]. DHEA levels also vary with gender, with higher levels in men than in women[1,54,65].

DEHYDROEPIANDROSTERONE SULFATE

Dehydroepiandrosterone sulfate (DHEA-s) is the sulfate ester of DHEA. This conversion is reversibly catalyzed by sulfotransferase (SULT2A1) primarily in the adrenals, the liver, and small intestine. In the blood, most DHEA is found as DHEA-s with levels that are about 300 times higher than those of free DHEA. Orally ingested DHEA is converted to its sulfate when passing through intestines and liver. Whereas DHEA levels naturally reach their peak in the early morning hours, DHEA-s levels show no diurnal variation. From a practical point of view, measurement of DHEA-s is preferable to DHEA, as levels are more stable.

Figure 14 - **DEHYDROEPIANDROSTERONE – BIOSYNTHESIS**



Adrenal steroidogenesis.

CYP11A1, side chain cleavage enzyme; CYP17A1, 17α-hydroxylase/17,20 lyase; POR, P450 oxidoreductase; ADX, adrenodoxin; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; CYP21A2, 21-hydroxylase; CYP11B1, 11β-hydroxylase; CYP11B2, aldosterone synthase; HSD11B1, 11β-hydroxysteroid dehydrogenase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; H6PDH, hexose-6-phosphate dehydrogenase; HSD17B, 17β-hydroxysteroid dehydrogenase; SRD5A, 5α-reductase; SULT2A1, DHEA sulfotransferase; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; PAPSS2, PAPS synthase type 2.

MECHANISM OF ACTION OF DHEA:

Although it predominantly functions as an endogenous precursor to more potent androgens such as testosterone and DHT, DHEA has been found to possess some degree of androgenic activity in its own right, acting as a low affinity (K_i = 1 μM), weak partial agonist of the androgen receptor. However, its intrinsic activity at the receptor is almost completely negligible, and on account of that, due to competition for binding with full agonists like testosterone, it actually behaves much more like an antagonist there, and hence, like an anti-androgen. However, its affinity for the receptor is very low, and for that reason, is unlikely to be of any significance under normal circumstances. In addition to its affinity for the androgen receptor, DHEA has also been found to bind to and activate the ER α and ER β estrogen receptors with K_i values of 1.1 μM and 0.5 μM, respectively, and EC_{50} values of >1 μM and 200 nM, respectively. Though it was found to be a partial agonist of the ER α with a maximal efficacy of 30-70%, the concentrations required for this degree of activation make it unlikely that the activity of DHEA at this receptor is physiologically meaningful. Remarkably however, DHEA acts as a full agonist of the ER β with a maximal response similar to or actually slightly greater than that of estradiol, and its levels in circulation and local tissues in the human body are high enough to activate the receptor to the same degree as that seen with circulating estradiol levels at somewhat higher than

their maximal, non-ovulatory concentrations; indeed, when combined with estradiol with both at levels equivalent to those of their physiological concentrations, overall activation of the ER β was doubled. As such, it has been proposed that DHEA may be an important and potentially major endogenous estrogen in the body[58,59].

Unlike the case of the androgen and estrogen receptors, DHEA does not bind to or activate the progesterone, glucocorticoid, or mineralocorticoid receptors. Other nuclear receptor targets of DHEA include the PPAR-α, PXR, and CAR. In addition, it has been found to directly act on several membrane receptors, including the NMDA receptor as a positive allosteric modulator, the $GABA_A$ receptor as a negative allosteric modulator, and the σ_1 receptor as an agonist. It is these actions that have conferred the label of a "neurosteroid" upon DHEA[47]. Finally, DHEA is thought to regulate a handful of other proteins via indirect, genomic mechanisms, including the enzymes P4502C11 and11β-HSD1—the latter of which is essential for the biosynthesis of the glucocorticoids such as cortisol and has been suggested to be involved in the anti-glucocorticoid effects of DHEA—and the carrier IGFBP1.

MEASUREMENT

As almost all DHEA is derived from the adrenal glands, blood measurements of DHEA / DHEA-s are useful to detect excess adrenal activity as seen in adrenal cancer or hyperplasia, including certain forms of congenital adrenal hyperplasia. Women with polycystic ovary syndrome tend to have high DHEA. Serum DHEA concentration exhibits a circadian rhythm that reflects the secretion of corticotropin (ACTH); they also vary during the menstrual cycle, being higher during the luteal phase. In contrast, serum DHEA sulfate concentrations do not exhibit a circadian rhythm because the plasma half-life of DHEA sulfate is much longer. DHEA and DHEA sulfate are derived from 17-hydroxypregnenolone and 17-hydroxyprogesterone. Their serum concentrations are, therefore, increased in conditions in which the concentration of these steroids is increased.

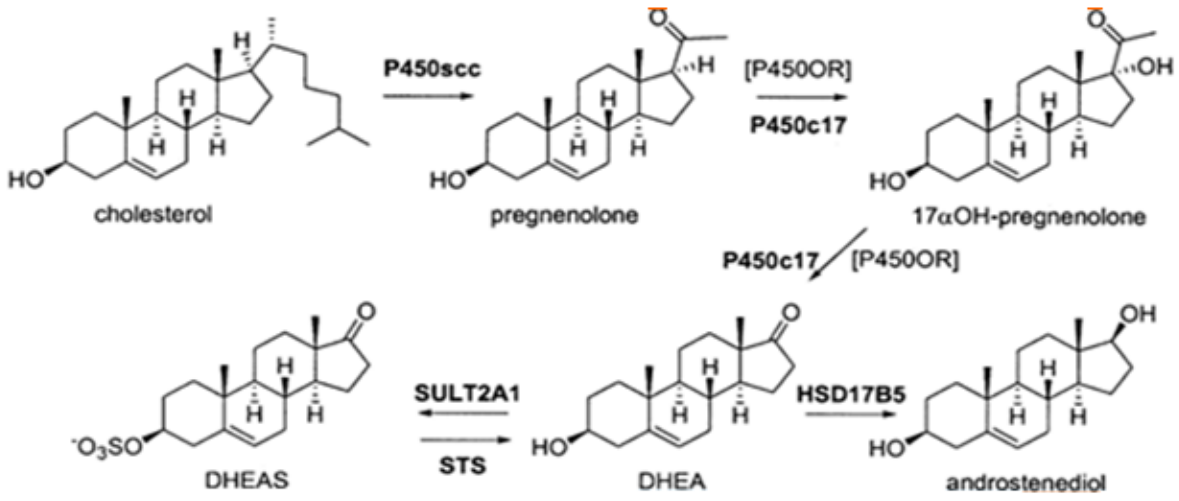


Figure 15 - **ENDOGENOUS PRODUCTION OF DHEA**

CHEMILUMINESCENCE IMMUNOASSAY: (CLIA)

CLIA is the one of the detection methods used in clinical laboratory. CLIA use chemiluminescent labels. Chemiluminescent molecules produce light when they are excited by chemical energy. Isoluminol and acridinium esters are the most commonly used as chemiluminescent labels.

Advantages of CLIA:

- Relatively quick.
- Economical.
- More sensitive compared to calorimetric method.

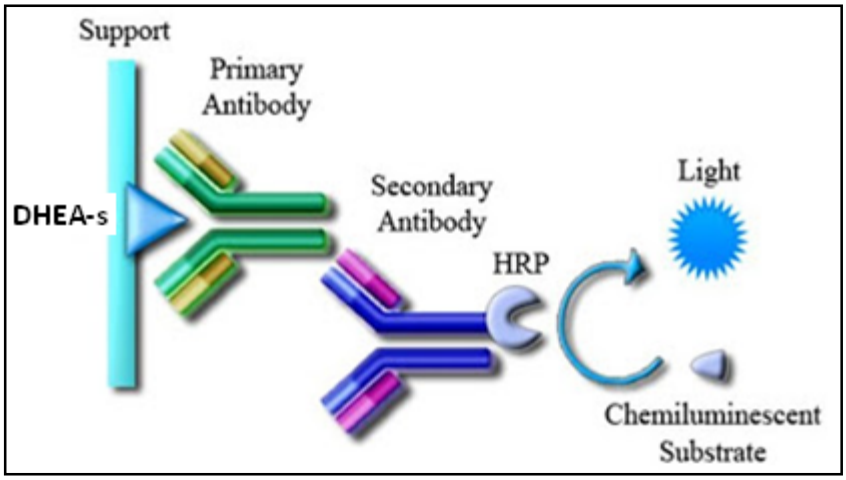


Figure 16 – **MEASUREMENT OF DHEAs BY CLIA METHOD**

DHEA-sulphate is estimated using CLIA method in this study.

Table 3 - **NORMAL RANGE OF DHEA-s**

AGE GROUP (yr)	**DHEA-s LEVEL (µg/dl)**	
	MALE	**FEMALE**
18-19	108 - 441	145 - 395
20-29	280 - 640	65 - 380
30-39	120 - 520	45 - 270
40-49	95 - 530	32 - 240
50-59	70 - 310	26 - 200
60-69	42 - 290	13 - 130
≥ 70	28 - 175	17 - 90

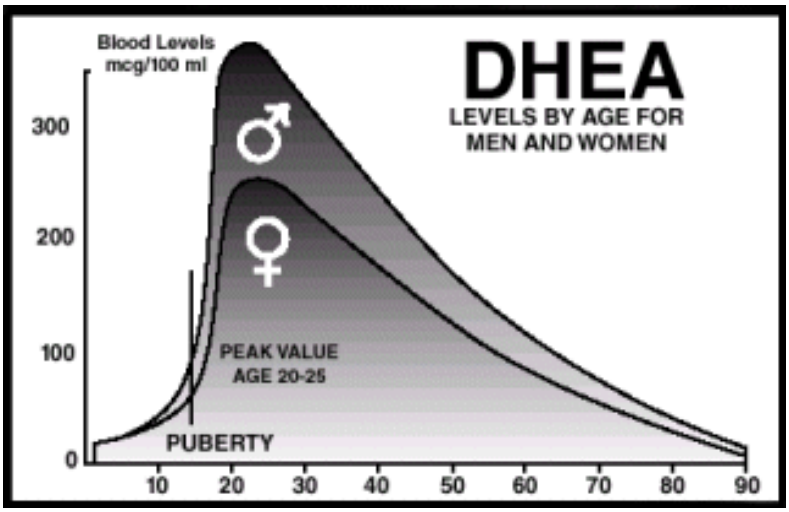


Figure 17 – **DHEA LEVELS WITH AGE**

INCREASING ENDOGENOUS PRODUCTION

Regular exercise is known to increase DHEA production in the body. Calorie restriction has also been shown to increase DHEA in primates. Some theorize that the increase in endogenous DHEA brought about by calorie restriction is partially responsible for the longer life expectancy known to be associated with calorie restriction.

ISOMERS

The term "dehydroepiandrosterone" is ambiguous chemically because it does not include the specific positions within epiandrosterone at which hydrogen atoms are missing. DHEA has a number of naturally occurring isomers that may have similar pharmacological effects. Some isomers of DHEA are 1-dehydroepiandrosterone and 4-dehydroepiandrosterone. These isomers are also technically DHEA, since they are dehydroepiandrosterones in which hydrogens are removed from the epiandrosterone skeleton.

EFFECTS AND USES

In women with adrenal insufficiency and the healthy elderly there is insufficient evidence to support the use of DHEA[19].

STRENGTH

Evidence is inconclusive with regards to the effect of DHEA on strength in the elderly[50]. In middle-aged men, no statistically significant effect of DHEA supplementation on lean body mass, strength, or testosterone levels was found in a randomized placebo-controlled trial[55]. One large (100 subjects) trial found no effect on strength following DHEA supplementation in the elderly group in the study. However, a small study suggested DHEA supplementation was associated with increases in free (but not total) testosterone levels. In postmenopausal women, within a randomized placebo-controlled trial, no statistically significant effect of DHEA supplementation on muscle strength was seen during a 12 week combined endurance and weight training program[56].

MEMORY

DHEA supplementation has not been found to be useful for memory function in normal middle aged or older adults[51,73]. It has been studied as a treatment for Alzheimer's disease, but there is no evidence that it is effective.

FEMALE REPRODUCTIVE HEALTH

Since 2000, DHEA supplementation has been used in reproductive medicine in combination with gonadotropins as a way to treat female infertility.

CARDIOVASCULAR DISEASE AND RISK OF DEATH

A review in 2003 found the then-extant evidence sufficient to suggest that low serum levels of DHEA-s may be associated with coronary heart disease in men, but insufficient to determine whether DHEA supplementation would have any cardiovascular benefit. A 2001 study found that a higher level of endogenous DHEA, as determined by a single measurement, correlated with a lower risk of death or cardiovascular disease[61,64,70]. However, a 2006 study found no correlation between DHEA levels and risk of cardiovascular disease or death in men. A 2007 study found that DHEA restored oxidative balance in diabetic patients, reducing tissue levels of pentosidine—a biomarker for advanced glycation endproducts.

LUPUS

There is some evidence of short term benefit in those with systemic lupus erythematosus but little evidence of long term benefit or safety[69].

SAFETY

DHEA is produced naturally in the human body, but the long term effects of its use are largely unknown. In the short term, several studies have noted few adverse effects. In a study by Chang et al., DHEA was administered at a dose of 200 mg/day for 24 weeks with slight androgenic effects noted. Another study utilized a dose up to 400 mg/day for 8 weeks with few adverse events reported. A longer term study followed patients dosed with 50 mg of DHEA for 12 months with the number and severity of side effects reported to be small. Another study delivered a dose of 50 mg of DHEA for 10 months with no serious adverse events reported.

As a hormone precursor, there has been a smattering of reports of side effects possibly caused by the hormone metabolites of DHEA. It is not known whether DHEA is safe for long-term use. Some researchers believe DHEA supplements might actually raise the risk of breast cancer, prostate cancer, heart disease, diabetes, and stroke. DHEA may stimulate tumor growth in types of cancer that are sensitive to hormones, such as some types of breast, uterine, and prostate cancer. DHEA may increase prostate swelling in men with benign prostatic hyperplasia (BPH), an enlarged prostate gland.

DHEA is a steroid hormone. High doses may cause aggressiveness, irritability, trouble sleeping, and the growth of body or facial hair on women. It

also may stop menstruation and lower the levels of HDL ("good" cholesterol), which could raise the risk of heart disease. Other reported side effects include acne, heart rhythm problems, liver problems, hair loss (from the scalp), and oily skin. It may also alter the body's regulation of blood sugar[60].

DHEA should not be used with tamoxifen, as it may promote tamoxifen resistance. Patients on hormone replacement therapy may have more estrogen-related side effects when taking DHEA. This supplement may also interfere with other medicines, and potential interactions between it and drugs and herbs should be considered.

DHEA is possibly unsafe for individuals experiencing the following conditions: pregnancy and breast-feeding, hormone sensitive conditions, liver problems, diabetes, depression or mood disorders, polycystic ovarian syndrome (PCOS) or cholesterol problems.

RESEARCH

CANCER

Some in vitro studies have found DHEA to have both anti-proliferative and apoptotic effect on cancer cell lines. The clinical significance of these findings, if any, is unknown. Higher levels of DHEA and other endogenous sex hormones

are strongly associated with an increased risk of developing breast cancer in both pre and postmenopausal women

LEGALITY

DHEA is legal to be sold in the United States as a dietary supplement. It is currently grandfathered in as an "Old Dietary Ingredient" being on sale prior to 1994. DHEA is specifically exempted from the Anabolic Steroid Control Act of 1990 and 2004. It is banned from use in athletic competition. DHEA and DHEA-s are readily available in the United States, where they are marketed as over-the-counter dietary supplements.

DHEA-s AND LONGEVITY: NEW CLUES FOR AN OLD FRIEND?

During the past five decades, a myriad of animal experiments has suggested that DHEA is a multifunctional hormone with immunoenhancing, anti-diabetic, antiobesity, anti-cancer, neurotropic, memory-enhancing, and anti-aging effects. Because a backdrop of these studies was conducted in rodents with little or no detectable circulating DHEA, it may be viewed as a pharmacological model with a naive environment that is devoid of endogenous DHEA.

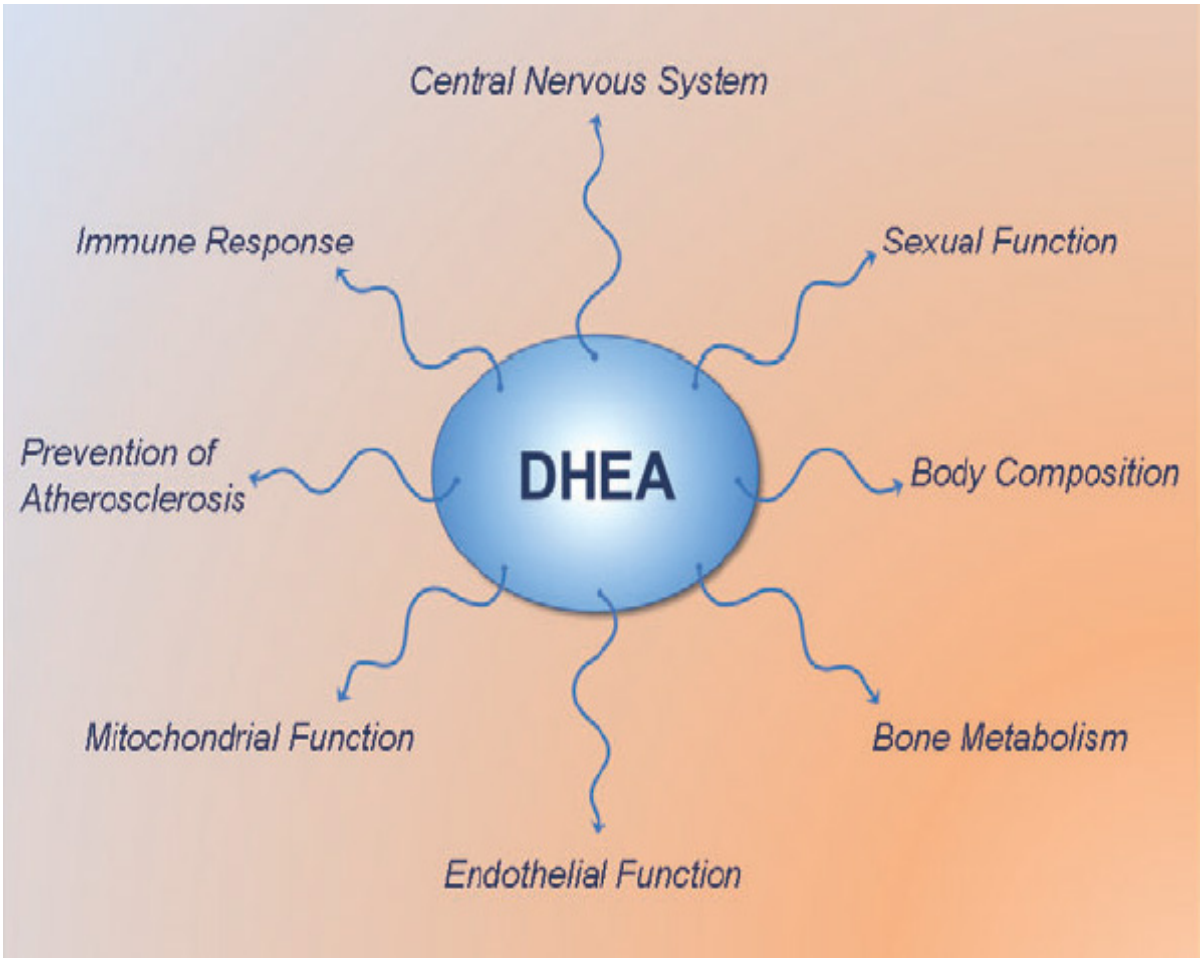


Figure 18 **– DHEA – PLEOTROPIC EFFECTS**

DHEA modulates endothelial function, reduces inflammation, improves insulin sensitivity, blood flow, cellular immunity, body composition, bone metabolism, sexual function, physical strength, provides neuroprotection, improves cognitive function, and memory enhancement. DHEA possesses 'pleiotropic' effects and reduced levels of DHEA and DHEA-s may be associated with a host of pathologies[67].

The secretion of DHEA by the human adrenal gland exhibits a pulsatile pattern with increasing frequency and amplitude at night. This pattern of DHEA synthesis and secretion by the zona reticularis is, in large measure, mediated by corticotrophin (ACTH) but without the feedback regulatory function. With aging, the progressive blunting of ACTH mediates pulsatile activities, particularly the nocturnal amplification of DHEA, without affecting the pulsatile rhythm of cortisol. Although the decline of DHEA-s levels persists into advanced age with a sexually dimorphic pattern, in contrast, cortisol levels in men and women show a parallel linear increase with aging. The age-related decline in DHEA-s shows marked individual differences with a wide range of values and is under partial hereditary control. It has been suggested that DHEA-s may be a measurable component of the individuality of the aging process itself.

In human aging, the reduction of adrenal androgen secretion is accompanied by a host of neuroendocrine–metabolic dysfunctions that include decline in the growth hormone-insulin-like growth factor I (GH-IGF-I) system, thyroid function, immune competence, fragmentation of sleep and neuronal loss. DHEA-s has a strong interrelation with functional activities observed in the oldest men in a study conducted by Ravaglia et al[60].

DHEA-s has also been shown to induce peroxisome gene expression mediated through the activation of peroxisome proliferator activated receptor-α

(PPAR-α), as reported by Peters et al. DHEA and α-Adiol are both inactive in this regard, suggesting the importance of 3β-sulfate that may be required for structural confirmation for PPAR-α. Thus, DHEA-s may serve as an important endogenous regulator of hepatic PPAR-α mediated pathways thereby maintain lipid homeostasis and prevent decline in cellular PPAR-α expression in normal aging.

The administration of DHEA-s to aging animals elicits a number of biologic changes that are mediated through a process involving PPAR-α activation with reversal of the dysregulated cytokines, particularly IL-6. In humans, James et al. and Straub et al. have provided evidence that serum levels of IL-6 increase with age and that serum DHEA-s levels are negatively correlated with serum IL-6 concentrations in both aging men and women[14]. The maximal effective dose of DHEA is in the range for immunomodulation. Thus, the increase in IL-6 production during the process of aging might be related to diminished DHEA-s secretion, which, in turn, may be a significant cofactor for the manifestation of inflammatory and age-related diseases, including bone loss.

INFLAMMAGING AND ANTI-INFLAMMAGING:

‘Inflamm-aging’ is the portmanteau word for inflammation and aging. A global reduction in the capacity to cope with a variety of stressors and a concomitant progressive increase in pro-inflammatory status are major

characteristics of the aging process. This phenomenon, which we will refer to as "inflamm-aging," is provoked by a continuous antigenic load and stress. A large part of the aging phenotype, including immunosenescence, is explained by an imbalance between inflammatory and anti-inflammatory networks, which results in the low grade chronic pro-inflammatory status. Within this perspective, healthy aging and longevity are likely the result, not only of a lower propensity to mount inflammatory responses but also of efficient anti-inflammatory networks, which in normal aging fail to fully neutralize the inflammatory processes consequent to the lifelong antigenic burden and exposure to damaging agents. Such a global imbalance can be a major driving force for frailty and common age-related pathologies.

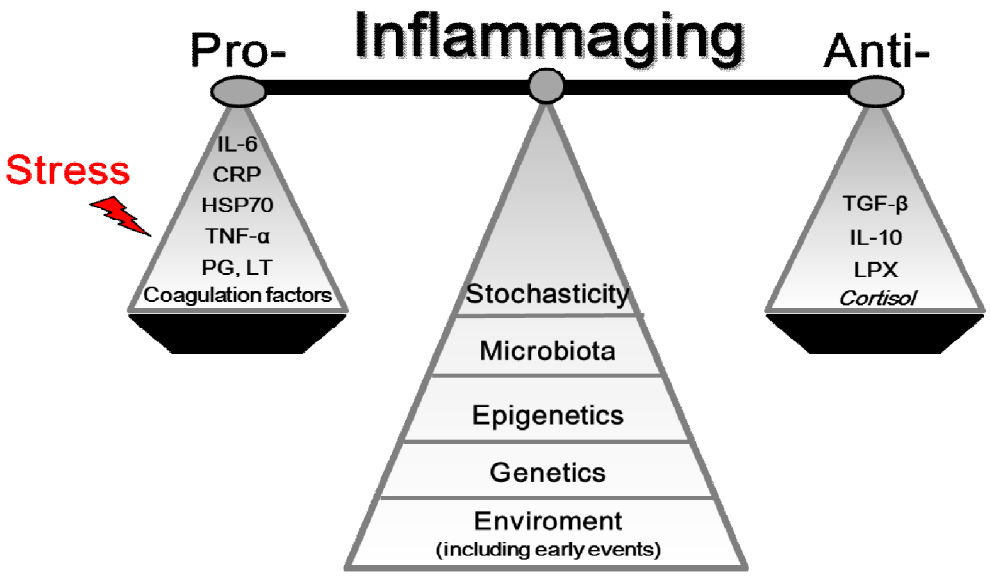


Figure 19 - **INFLAMMAGING**

The rate of reaching the threshold of pro-inflammatory status over which diseases/disabilities ensue and the individual capacity to cope with and adapt to stressors are assumed to be complex traits with a genetic component. The persistence of inflammatory stimuli over time represents the biologic background favoring the susceptibility to age-related diseases/disabilities. To conclude, the beneficial effects of inflammation devoted to the neutralization of harmful agents early in life and in adulthood become detrimental late in life.

MATERIALS AND METHODS

Study Centre: Geriatric ward (Male & Female) in Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai.

Ethical Committee approval: Ethical Committee clearance obtained from Institutional Ethics Committee of Madras Medical College held on 03-06-2014.

Study Design: Hospital based Observational study.

Duration of the Study: 3 months. (from June 2014 to August 2014)

Sample Size: 100 patients.

Inclusion Criteria:

- Subjects - 65 years of age or above.
- Those who are willing to participate & co-operative for the study.

Exclusion Criteria:

- Patients who are not willing to consent.
- Critically ill patients who are not able to participate.
- H/O use of DHEA, androgen or estrogen in the preceding year.
- H/O Adrenal insufficiency / tumour.
- H/O Breast cancer / Prostate cancer.

Details of the study:

Patients were selected as per the above mentioned inclusion and exclusion criteria. Relevant history was obtained. Anthropometric evaluation was done. Fried's criteria was employed to assess the frailty phenotype. It comprises of 5 components. They are-

1) Self-reported weight loss.
2) Grip strength measured by hand dynamometer.
3) Sense of exhaustion – self reported.
4) 15 ft walking speed.
5) Physical activity assessed by Minnesota Leisure time activity questionnaire. (short version)

Patients were categorized into 3 groups based on the number of frailty components.

- FRAIL ($\geq$ 3 characteristics)
- INTERMEDIATE FRAIL (1-2 characteristics)
- NON-FRAIL (no characteristic)

33 frail, 34 intermediate frail and 33 non-frail patients were selected by Stratified random sampling method. Blood samples of patients from each group were collected and serum DHEA-s level was estimated. (using CLIA method)

Informed consent was obtained from all study participants.

Table 4 - **FRIED'S CRITERIA**

CHARACTERISTICS	CUT OFFS
1) Weight loss	Baseline: Lost > 10 pounds unintentionally in last year (5% of previous year's body weight)
2) Exhaustion CES-D	Self report of either of: i) felt that everything I did was an effort in the last week ii) could not get going in the last week
3) Low Physical Activity Minnesota LTA questionnaire	Women: Kcal/wk < 270 on activity scale Men: Kcal/wk < 383 on activity scale
4) Slowness Walking 15 ft (4.57m) at usual pace	Women: time ≥ 7 s for height ≤ 159 cm time ≥ 6 s for height > 159 cm Men: time ≥ 7 s for height ≤ 173 cm time ≥ 6 s for height > 173 cm
5) Weakness Grip strength	Women: ≤ 17 kg for BMI ≤ 23 ≤ 17.3 kg for BMI 23.1 - 26 ≤ 18 kg for BMI 26.1 - 29 ≤ 21 kg for BMI > 29 Men: ≤ 29 kg for BMI <= 24 ≤ 30 kg for BMI 24.1 - 26 ≤ 30 kg for BMI 26.1 - 28 ≤ 32 kg for BMI > 28

Figure 20 - **HAND DYNAMOMETER FOR ASSESSMENT OF GRIP STRENGTH**

Table 5 - **SHORT VERSION OF MINNESOTA LEISURE TIME PHYSICAL ACTIVITY QUESTIONNAIRE**

ACTIVITIES	**PERFORMED (YES/NO)**	**TIME (Min/Week)**	**CALCULATED (Kcal/week)**
Walking for pleasure			
Walking to & from work			
Using stairs when elevator is available			
Back packing			
Mountain climbing			
Bicycling			
Dancing			
Home exercise			
Health club			
Jogging			
Running			
Weight lifting			
Lawn & garden activities			
Sports			
Miscellaneous			

Statistical analysis:

Descriptive statistics (mean ± standard deviation or count/proportion) were calculated for each study variable.

A contingency table was created to summarise variation in the frequency of frailty categories (0 = Non-Frail, 1–2 = Intermediate Frail and 3–5 = Frail) relative to DHEA-s quartiles (15.0–27.4, 27.5–46.4, 46.5–78.4 and ≥ 78.5 μg/dL). The Pearson $\chi 2$ test was applied to assess the statistical significance of the relationship between frailty categories and DHEA-s levels.

The potential that either an observed association or lack of association between frailty and DHEA-s could be due to confounding by other subject characteristics was evaluated. The Pearson $\chi 2$ test was applied to investigate relationships between frailty and these other characteristics age (65–74, 75–84, ≥ 85), gender and body mass index (≤ 24, 24-29, ≥ 29)

Multivariable ordinal logistic regression was used to establish the relationship between frailty and DHEA-s while controlling for the potential confounding effects of other subject characteristics. Frailty was the dependent variable in the modelling process. DHEA-s was the primary independent variable.

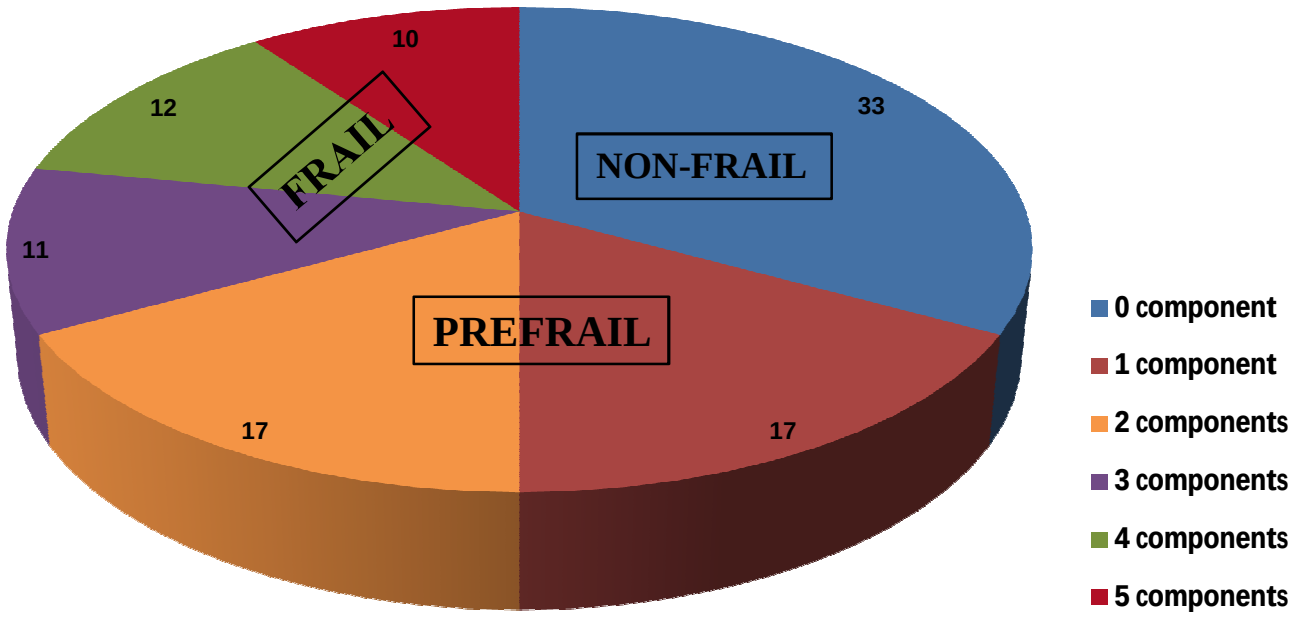
Analyses were performed using the XLSTAT 2014 software package. A 5% threshold was used for declaring a statistical significance in all tests.

RESULTS

Of the 100 study subjects, 53 were male and 47 were female. The mean age of the study population was 77.12 yr (SD=± 6.79 yr). The mean DHEA-s level was 49.55 ± 24.97 µg/dl. Descriptive statistics of the study is tabulated. (Table 6)

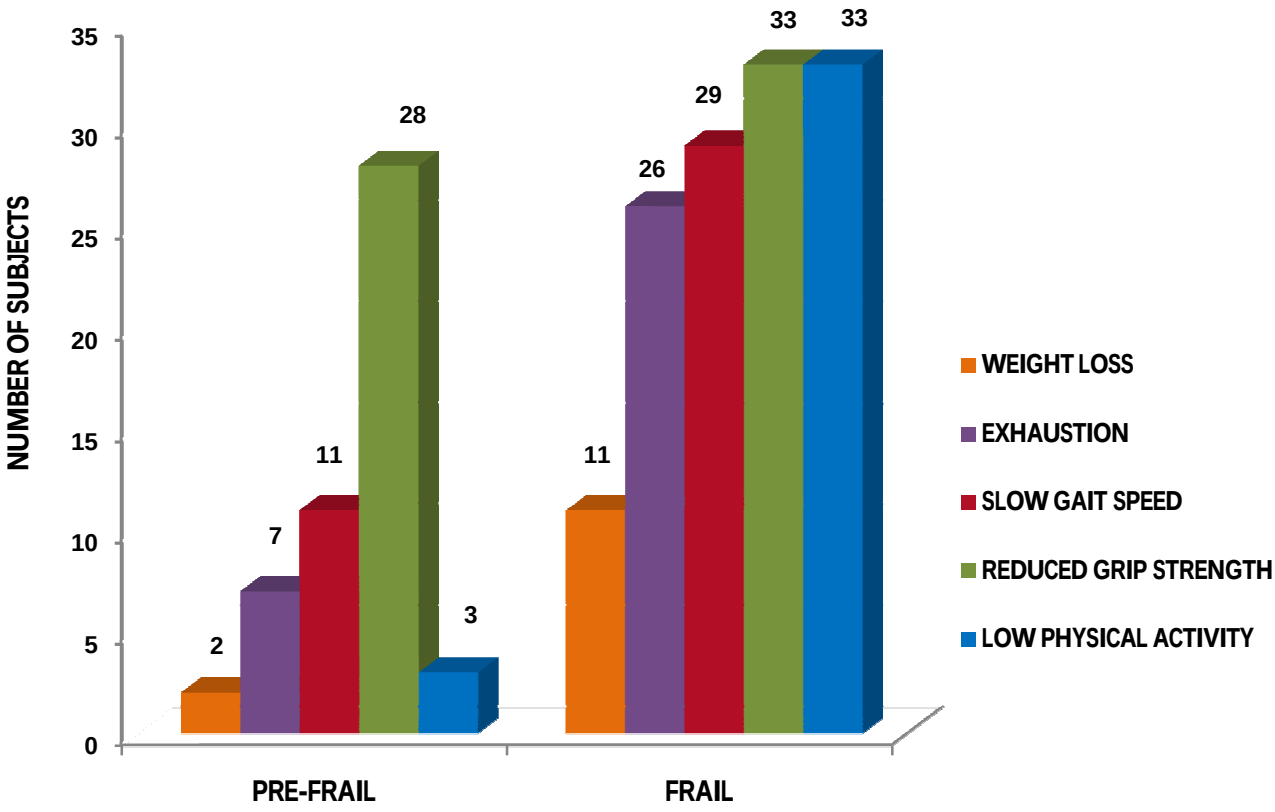
CHARACTERISTICS OF STUDY SUBJECTS	MEAN ± SD (or) COUNTS/%
Gender	
Male	53/53%
Female	47/47%
Age (yr)	77.12 ± 6.79
BMI (kg/m²)	25.08 ± 3.10
DHEA-s (*µ*g/dL)	49.55 ± 24.97
Frailty assessment components	
15-ft walking speed (m/s)	0.70 ± 0.18
Physical activity (kcal/wk)	1254 ± 1092
Handgrip strength (kg)	14.82 ± 9.35
Weight loss	13/13%
Exhaustion	33/33%
Number of frailty components	
0 (non-frail)	33/33%
1 (intermediate)	17/17%
2 (intermediate)	17/17%
3 (frail)	11/11%
4 (frail)	12/12%
5 (frail)	10/10%

Chart 1 - **DISTRIBUTION OF NUMBER OF FRAILTY COMPONENTS**



Of the 34 intermediate frail subjects, 17 had one frailty component and 17 had two frailty components. In the frail category, 11 had 3 frail characteristics, 12 had 4 characteristics and 10 had all 5 characteristics.

Chart 2 - **FREQUENCY DISTRIBUTION OF INDIVIDUAL FRAILTY COMPONENTS**



Reduced grip strength is the common frail characteristic observed among the pre-frail subjects, followed by slow gait speed. Reduced grip strength & low physical activity were invariably noted in the frail group followed by slow gait speed & exhaustion.

Table 7 – **DESCRIPTIVE STATISTICS OF FRAILTY CATEGORIES**

PARAMETER	NON-FRAIL	INTERMEDIATE	FRAIL
No of subjects (n)	33	34	33
Age (yr)	74.85 ± 7.12	76.35 ± 6.03	80.18 ± 6.20
Height (cm)	159.48 ± 7.99	154.41 ± 6.90	151.61 ± 5.56
Weight (kg)	62.48 ± 9.34	61.43 ± 7.04	57.41 ± 9.58
BMI (kg/m^2)	24.48 ± 2.37	25.79 ± 2.73	24.95 ± 3.98
Gait speed (m/s)	0.84 ± 0.08	0.74 ± 0.17	0.53 ± 0.14
Grip strength (kg)	25.30 ± 6.37	11.85 ± 6.21	7.39 ± 3.44
DHEA-s level (µg/dl)	64.42 ± 22.54	47.99 ± 22.12	36.28 ± 21.72

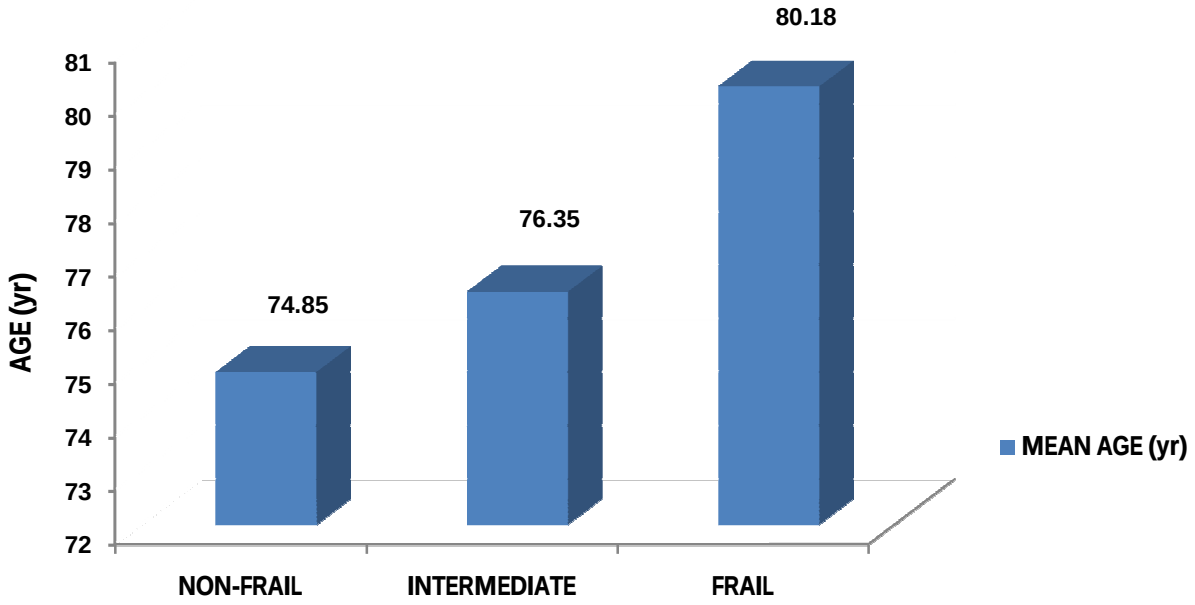
The mean ± SD of the study variables of each category is tabulated. The frailty phenotype increased with advancing age. The mean DHEA-s level was the lowest among the frail group.

Table 8 - **DESCRIPTIVE STATISTICS OF FRAILTY CATEGORIES (GENDER BASED)**

PARAMETER	NON-FRAIL		INTERMEDIATE		FRAIL	
	MALE	**FEMALE**	**MALE**	**FEMALE**	**MALE**	**FEMALE**
No of subjects (n)	18	15	18	16	17	16
Age (yr)	75 ± 7.20	74.67 ± 6.92	76.56 ± 6.46	76.13 ± 6.02	80.41 ± 6.14	79.94 ± 6.61
Height (cm)	163.72 ± 6.65	154.40 ± 5.57	159.78 ± 3.28	148.38 ± 4.86	155.24 ± 4.16	147.75 ± 4.01
Weight (kg)	66.83 ± 8.13	57.27 ± 7.03	64.39 ± 4.34	58.09 ± 7.93	60.03 ± 9.39	54.63 ± 9.70
BMI (kg/m^2)	24.90 ± 2.37	23.96 ± 2.08	25.26 ± 2.08	26.38 ± 3.25	24.91 ± 3.78	25.01 ± 4.36
Gait speed (m/s)	0.89 ± 0.06	0.78 ± 0.05	0.78 ± 0.19	0.69 ± 0.12	0.57 ± 0.17	0.50 ± 0.08
Grip strength (kg)	29.5 ± 4.31	20.27 ± 4.50	11.67 ± 5.49	12.06 ± 6.95	9.29 ± 2.85	5.38 ± 2.80
DHEA-s level (µg/dl)	65.93 ± 21.13	62.61 ± 23.82	49.21 ± 22.59	46.61 ± 22.17	35.24 ± 23.20	37.38 ± 23.34

The mean ± SD of study variables of each group (according to gender) is tabulated. The mean DHEA-s level did not vary much across the sexes.

Chart 3 - **MEAN AGE OF STUDY GROUPS**

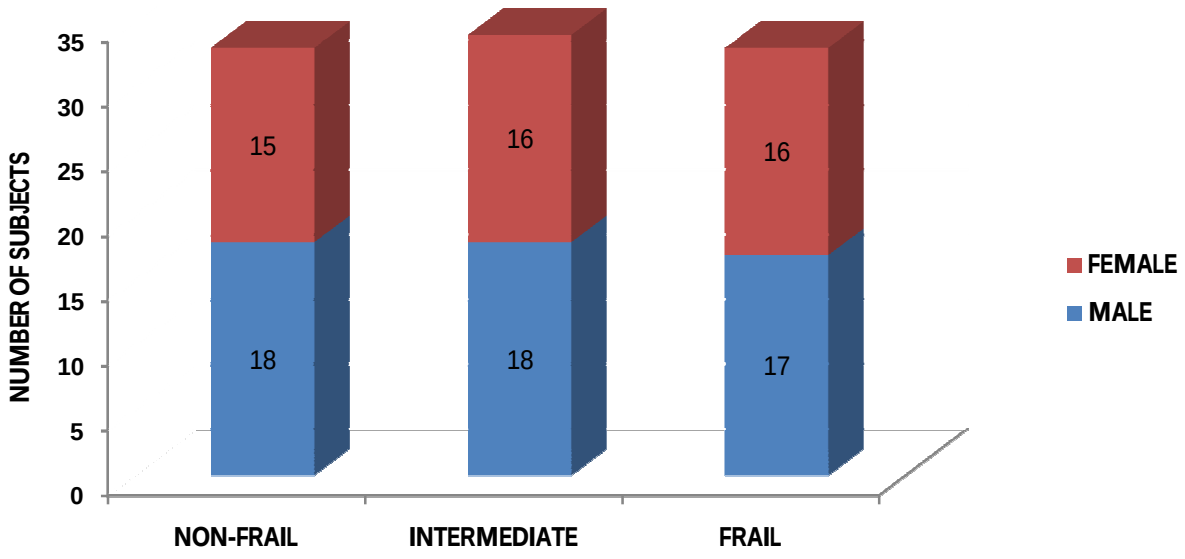


The mean age of the frail group was 80.18 yrs and that of the non-frail group was 74.85 yrs. The ANOVA test revealed a statistical significance between the mean age of the frailty categories. **(p < 0.0001)**

Table 9 - **MEAN AGE OF STUDY GROUPS**				
AGE	**NON-FRAIL**	**INTERMEDIATE**	**FRAIL**	**p-VALUE**
MEAN (yr)	74.85	76.35	80.18	**< 0.0001***
SD (yr)	7.12	6.03	6.20	

***** statistically significant.

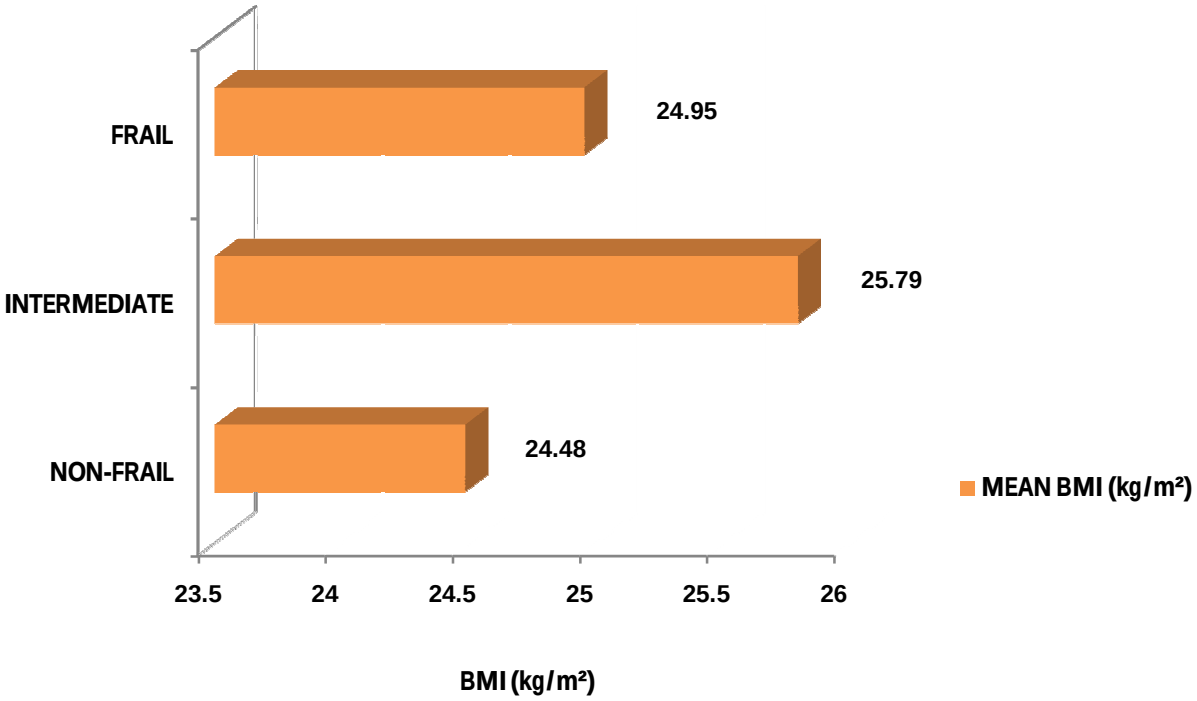
Chart 4 - **SEX DISTRIBUTION AMONG STUDY GROUPS**



32% (17) of males were frail compared to 34% (16) females. Similar percents were noted among non-frail males and females. The test did not reveal any statistical significance between both sexes with regards to frailty category. **(p=0.97)**

Table 10 - **SEX DISTRIBUTION AMONG STUDY GROUPS**					
GENDER	**NON-FRAIL**	**INTERMEDIATE**	**FRAIL**	**TOTAL**	**p-value**
MALE	18	18	17	53	
FEMALE	15	16	16	47	**0.97**
TOTAL	33	34	33	100	

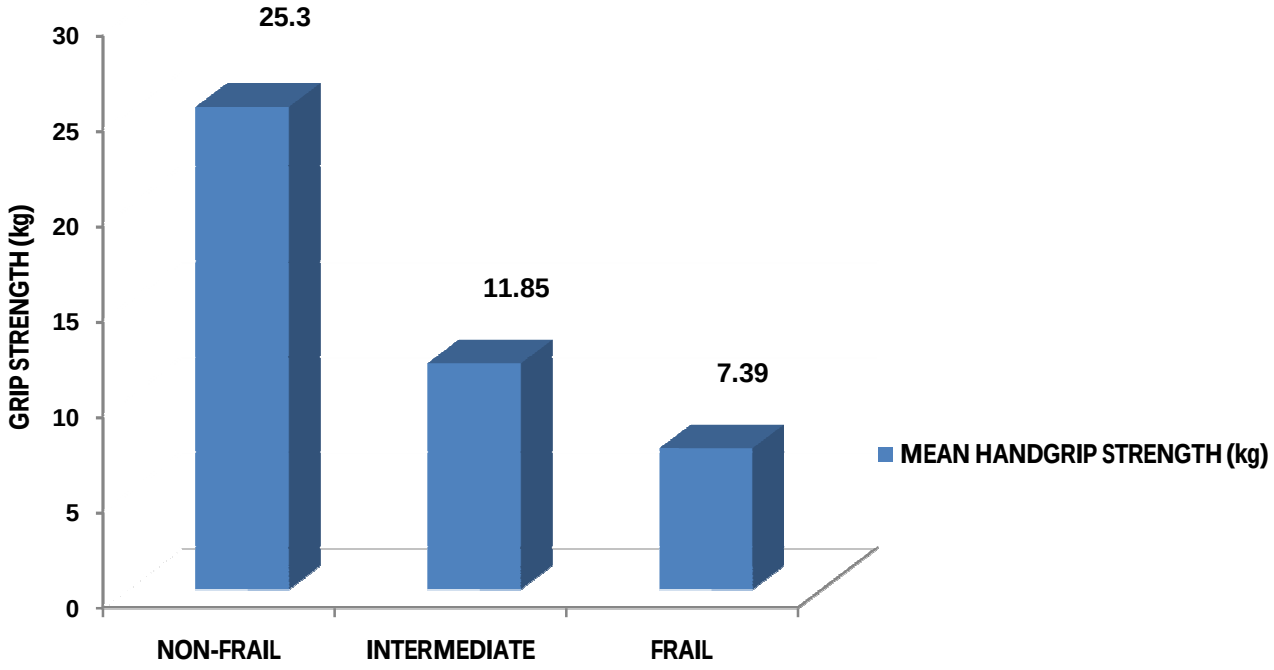
Chart 5 - **MEAN BMI OF STUDY GROUPS**



There was no statistical significance between the mean BMI of the study groups. **(p = 0.99)**

Table 11 - **MEAN BMI OF STUDY GROUPS**				
BMI	**NON-FRAIL**	**INTERMEDIATE**	**FRAIL**	**p-VALUE**
MEAN (kg/m²)	24.48	25.79	24.95	**0.99**
SD (kg/m²)	2.37	2.73	3.98	

Chart 6 - **MEAN HANDGRIP STRENGTH OF STUDY GROUPS**



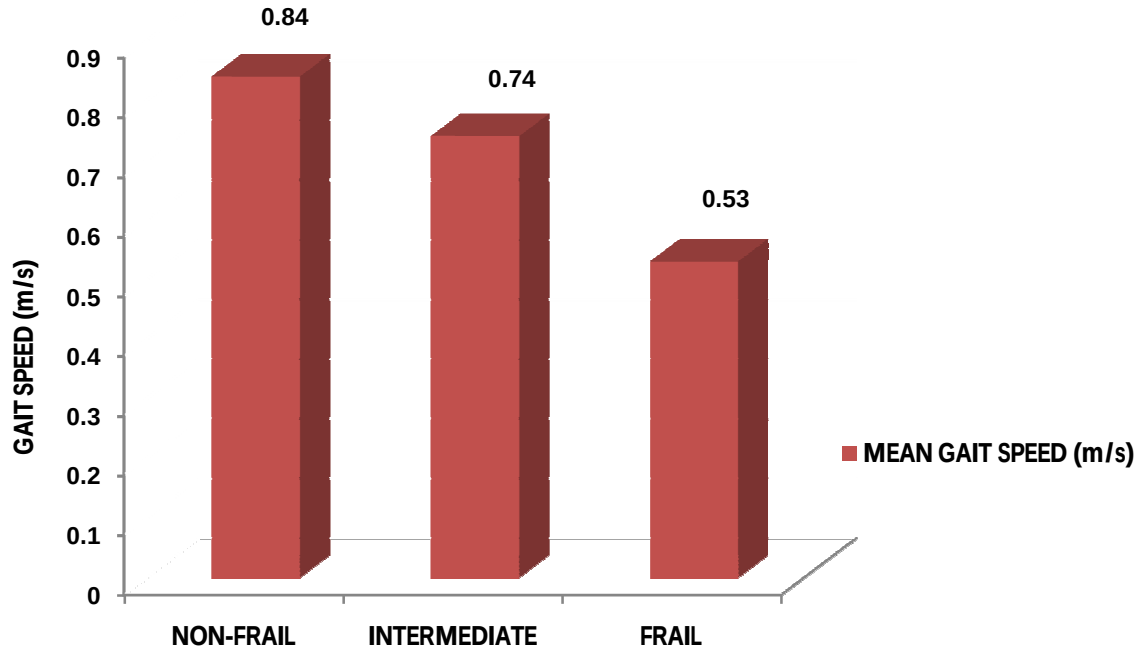
The mean grip strength of non-frail group was 25.3 kg whereas it was as low as 7.39 kg among frail group. There was a statistical difference between the mean grip strength of the frailty categories. **(p < 0.0001)**

Table 12 - **MEAN HANDGRIP STRENGTH OF STUDY GROUPS**

GRIP STRENGTH	NON-FRAIL	INTERMEDIATE	FRAIL	p-VALUE
MEAN (kg)	25.3	11.85	7.39	**< 0.0001***
SD (kg)	6.37	6.21	3.44	

*statistically significant.

Chart 7 - **MEAN GAIT SPEED OF STUDY GROUPS**



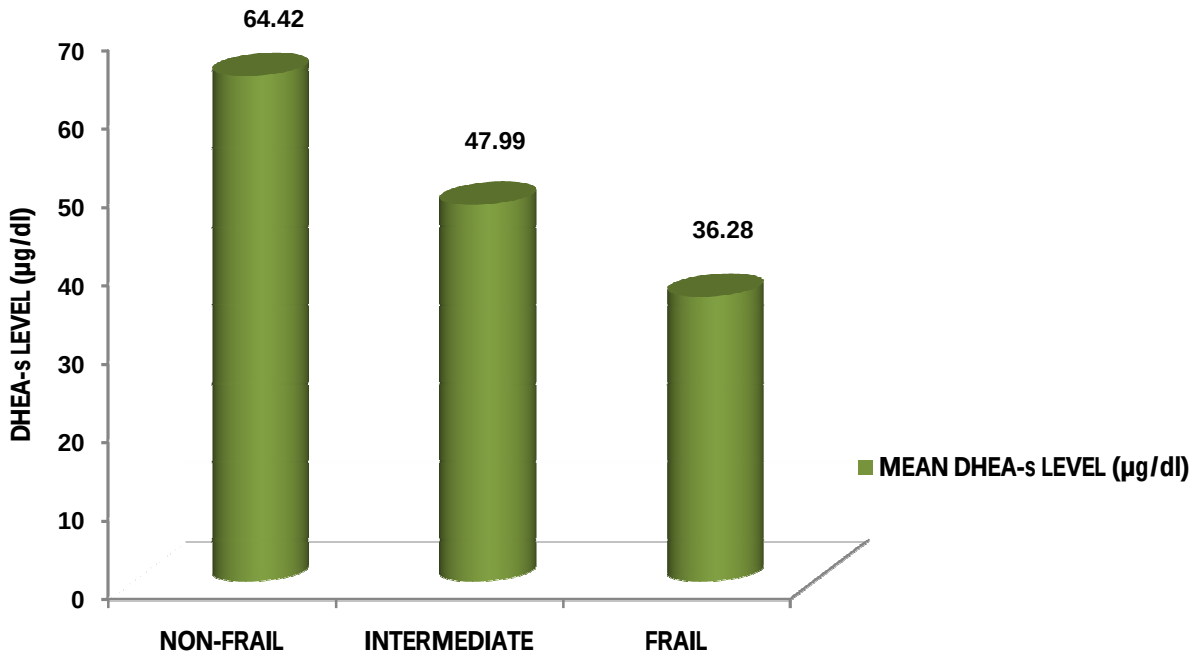
The mean gait speed of the non-frail group was 0.84 m/s and 0.53 m/s for the frail group. There was a statistical difference between the mean gait speed of the frailty categories. **(p < 0.0002)**

Table 13 - **MEAN GAIT SPEED OF STUDY GROUPS**

GAIT SPEED	**NON-FRAIL**	**INTERMEDIATE**	**FRAIL**	**p-VALUE**
MEAN (m/s)	0.84	0.74	0.53	**< 0.0002***
SD (m/s)	0.08	0.17	0.14	

***** statistically significant.

Chart 8 - **MEAN DHEA-s LEVEL OF STUDY GROUPS**



The DHEA-s level decreased as the magnitude of frailty increased. The mean level of DHEA-s of the non-frail group was 64.42 µg/dl and 36.28 µg/dl for the frail group. There was a statistical difference between the mean DHEA-s level of the frailty categories. **(p < 0.002)**

Table 14 - **MEAN DHEA-s LEVEL OF STUDY GROUPS**				
DHEA-s LEVEL	**NON-FRAIL**	**INTERMEDIATE**	**FRAIL**	**p-VALUE**
MEAN (µg/dl)	64.42	47.99	36.28	**< 0.002***
SD (µg/dl)	22.54	22.12	21.72	

***** statistically significant.

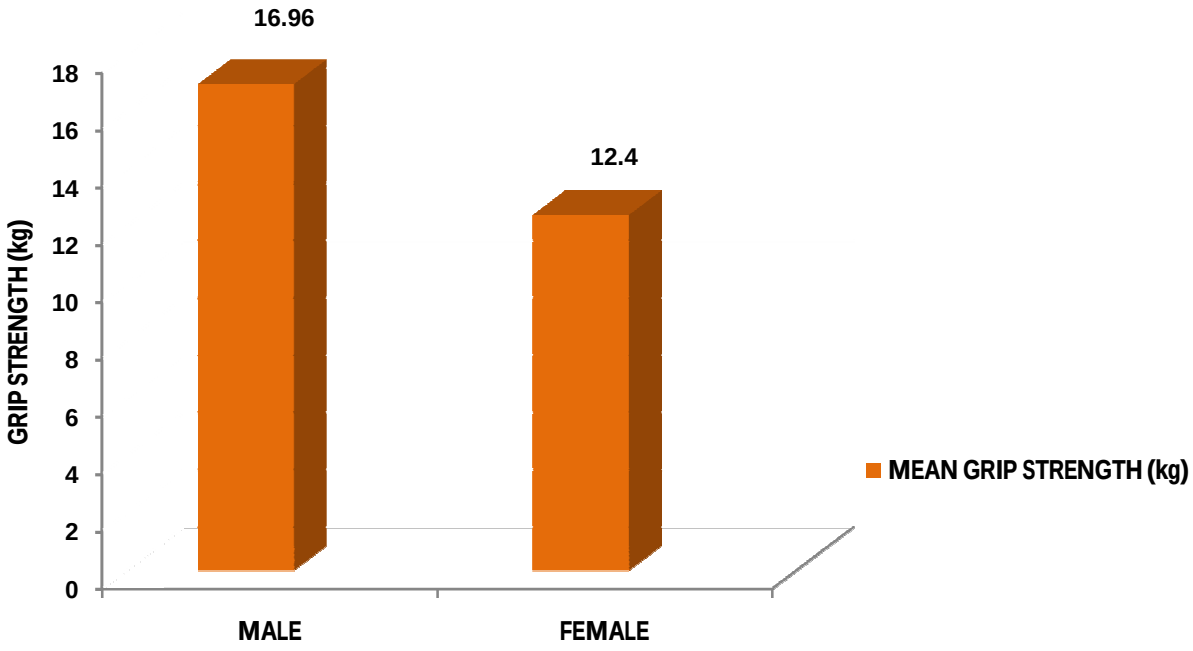
Table 15 - **DESCRIPTIVE STATISTICS BASED ON GENDER**

PARAMETER	OVERALL	MALE	FEMALE
No of subjects (n)	100	53	47
Age (yr)	77.12 ± 6.79	77.26 ± 6.88	76.96 ± 6.76
Height (cm)	155.16 ± 7.50	159.66 ± 5.95	150.09 ± 5.60
Weight (kg)	60.45 ± 8.82	63.82 ± 7.93	56.65 ± 8.28
BMI (kg/m^2)	25.08 ± 2.37	25.02 ± 2.77	25.14 ± 3.46
Gait speed (m/s)	0.70 ± 0.18	0.75 ± 0.20	0.65 ± 0.15
Grip strength (kg)	14.82 ± 9.35	16.96 ± 10.09	12.40 ± 7.86
DHEA-s level (µg/dl)	49.55 ± 24.97	50.41 ± 25.25	48.57 ± 24.89

The mean ± SD of the study variables is tabulated according to gender.

The gait speed & grip strength varied between the sexes but the DHEA-s level did not vary.

Chart 9 - **MEAN GRIP STRENGTH OF SEXES**

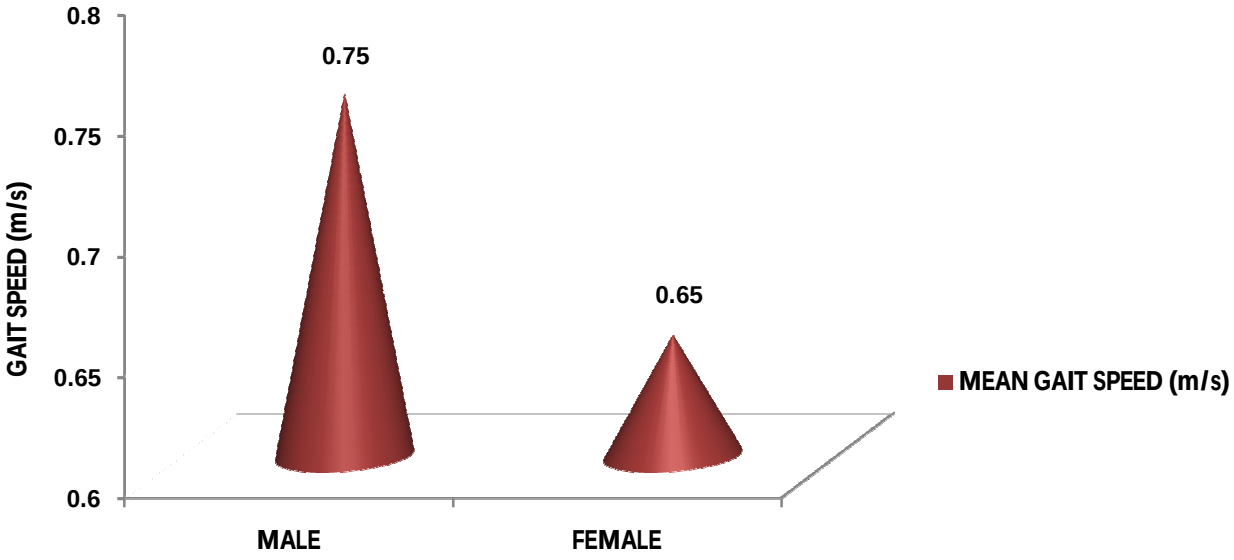


The mean grip strength of males was 16.96 kg whereas it was 12.4 kg among females. There was a statistically significant difference between the mean grip strength of both sexes. **(p < 0.004)**

Table 16 - **MEAN GRIP STRENGTH OF SEXES**			
GRIP STRENGTH	**MALE**	**FEMALE**	**p-VALUE**
MEAN (kg)	16.96	12.4	**< 0.004***
SD (kg)	10.09	7.86	

***** statistically significant.

Chart 10 - **MEAN GAIT SPEED OF SEXES**



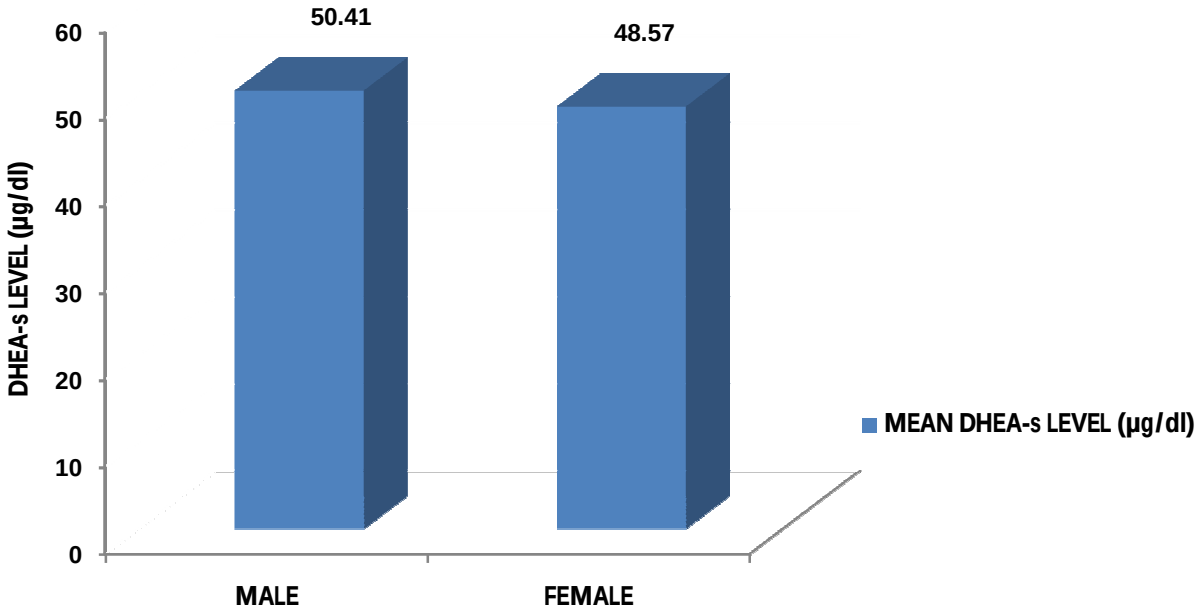
The mean gait speed of males was 0.75 m/s and 0.65 m/s for females . There was a statistically significant difference between the mean gait speed of both sexes.

(p < 0.04)

Table 17 - **MEAN GAIT SPEED OF SEXES**			
GAIT SPEED	**MALE**	**FEMALE**	**p-VALUE**
MEAN (m/s)	0.75	0.65	**< 0.04***
SD (m/s)	0.20	0.15	

***** statistically significant.

Chart 11 - **MEAN DHEA-s LEVEL OF SEXES**



The mean DHEA-s level of males was 50.41 µg/dl and 48.57 µg/dl for females. There was no statistical difference between the mean DHEA-s level of both sexes. **(p = 0.93)**

Table 18 - **MEAN DHEA-s LEVEL OF SEXES**

DHEA-s LEVEL	**MALE**	**FEMALE**	**p-VALUE**
MEAN (µg/dl)	50.41	48.57	**0.93**
SD (µg/dl)	25.25	24.89	

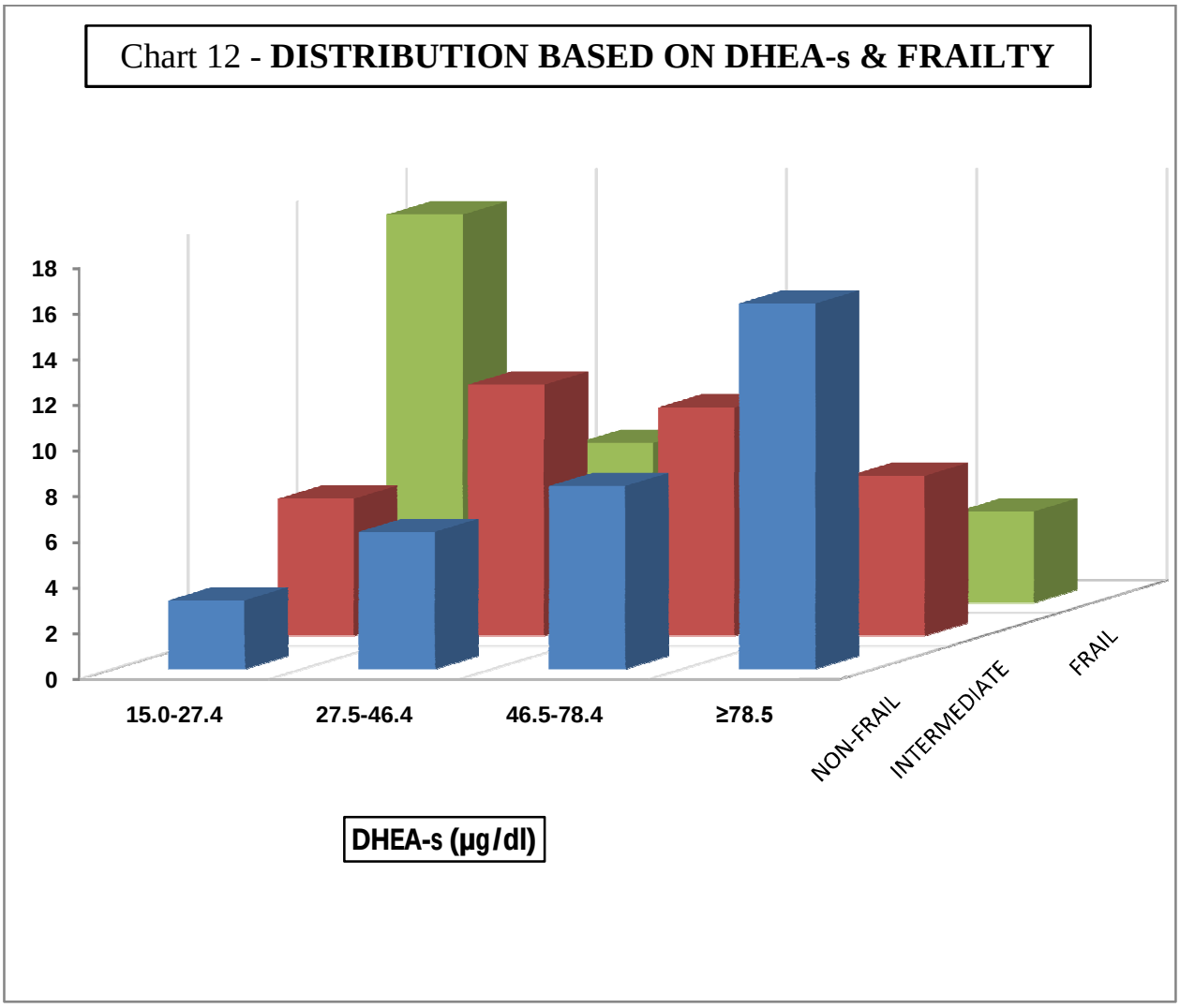
DHEA-s level & Frailty categories:

A cross-tabulation of frailty categories by DHEA-s quartiles suggested a significant association between the two variables **(p < 0.0004)**. 16% of subjects in the highest quartile of DHEA-s values had zero frailty components. This percentage consistently decreased (16% vs 7% vs 4%) as the frailty phenotype increased. Conversely, the percentage of subjects classified as frail increased from the highest quartile to the lowest. (4% vs 5% vs 7% vs 17%).

Table 19 - **DHEA-s LEVEL & FRAILTY CATEGORIES**

DHEA-s quartile (µg/dl)	**NON-FRAIL**		**INTERMEDIATE**		**FRAIL**		**TOTAL**	**p-value**
	MALE	**FEMALE**	**MALE**	**FEMALE**	**MALE**	**FEMALE**		
15.0 - 27.4	1	2	3	3	9	8	26	**0.0004***
27.5 - 46.4	4	2	6	5	3	4	24	
46.5 - 78.4	5	3	5	5	3	2	23	
≥ 78.5	8	8	4	3	2	2	27	
TOTAL	18	15	18	16	17	16	100	
	33		34		33			

*statistically significant.



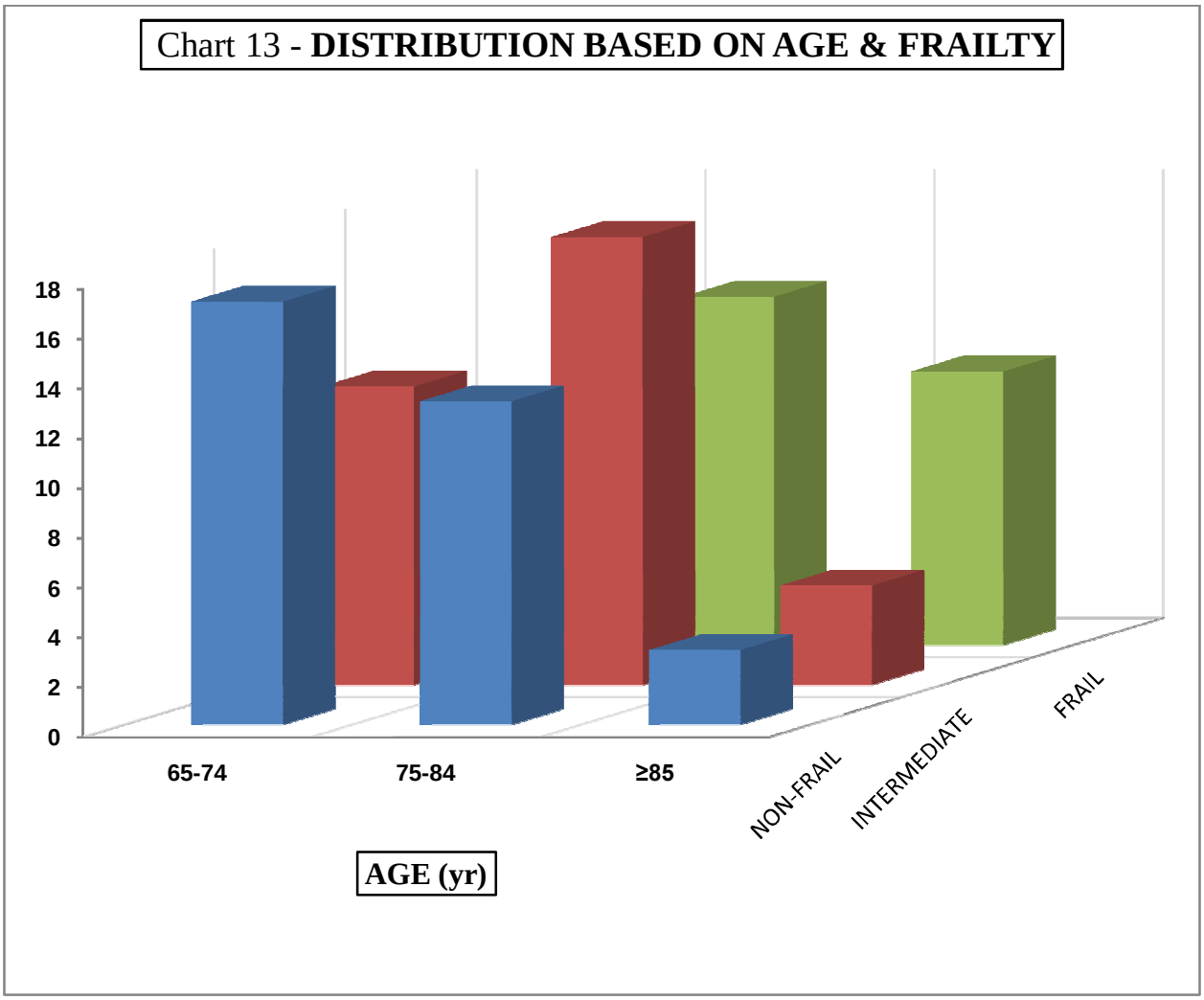
This chart depicts the frequency distribution based on DHEA-s quartiles & Frailty categories. It is obvious from the chart that the frequencies of non-frail with high DHEA-s level and frail with low DHEA-s level are high portraying an inverse association between the two variables.

Age group & Frailty categories:

Table 20 - **AGE GROUP & FRAILTY CATEGORIES**								
AGE (yr)	**NON-FRAIL**		**INTERMEDIATE**		**FRAIL**		**TOTAL**	**p-value**
	MALE	**FEMALE**	**MALE**	**FEMALE**	**MALE**	**FEMALE**		
65-74	9	8	6	6	4	4	37	**0.03***
75-84	7	6	10	8	7	7	45	
≥85	2	1	2	2	6	5	18	
TOTAL	18	15	18	16	17	16	100	
	33		34		33			

***statistically significant.

In the ≥ 85 age group,11 out of 18 (61%) were frail compared to 3 out of 18 (17%) who were non-frail, whereas in the 65-74 age group, only 8 out of 37 (22%) were frail compared to 17 out of 37 (46%) who were non-frail. The Chi-square test denotes a significant difference between the two variables. **(p < 0.03)**

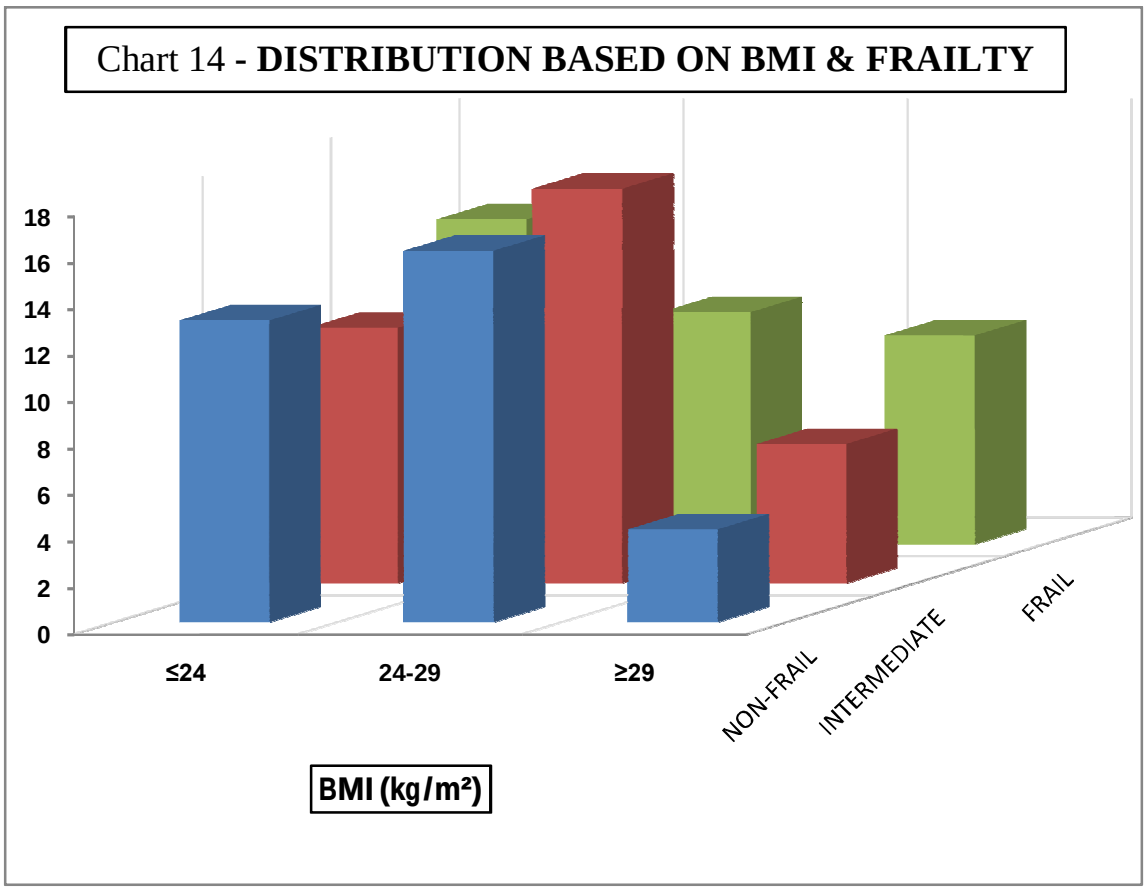


With increase in age, the transition from non-frail to frail becomes evident. The frequencies of non-frail are highest and lowest among the young old (65-74 yr) and oldest old (≥ 85 yr) respectively.

BMI and Frailty categories:

Table 21 - **BMI AND FRAILTY CATEGORIES**								
BMI (kg/m²)	**NON-FRAIL**		**INTERMEDIATE**		**FRAIL**		**TOTAL**	**p-value**
	MALE	**FEMALE**	**MALE**	**FEMALE**	**MALE**	**FEMALE**		
≤ 24	7	6	6	5	7	7	38	**0.36**
24 - 29	8	8	9	8	6	4	43	
≥ 29	3	1	3	3	4	5	19	
TOTAL	18	15	18	16	17	16	100	
	33		34		33			

There was no significant association between BMI and frailty categories. **(p=0.36)**



Though there was no significant association between BMI & frailty categories, there was a significant DHEAs–BMI interaction that affected the former's relation with frailty. The modelling process revealed that the magnitude of the association between frailty and DHEA-s was dependent on BMI.

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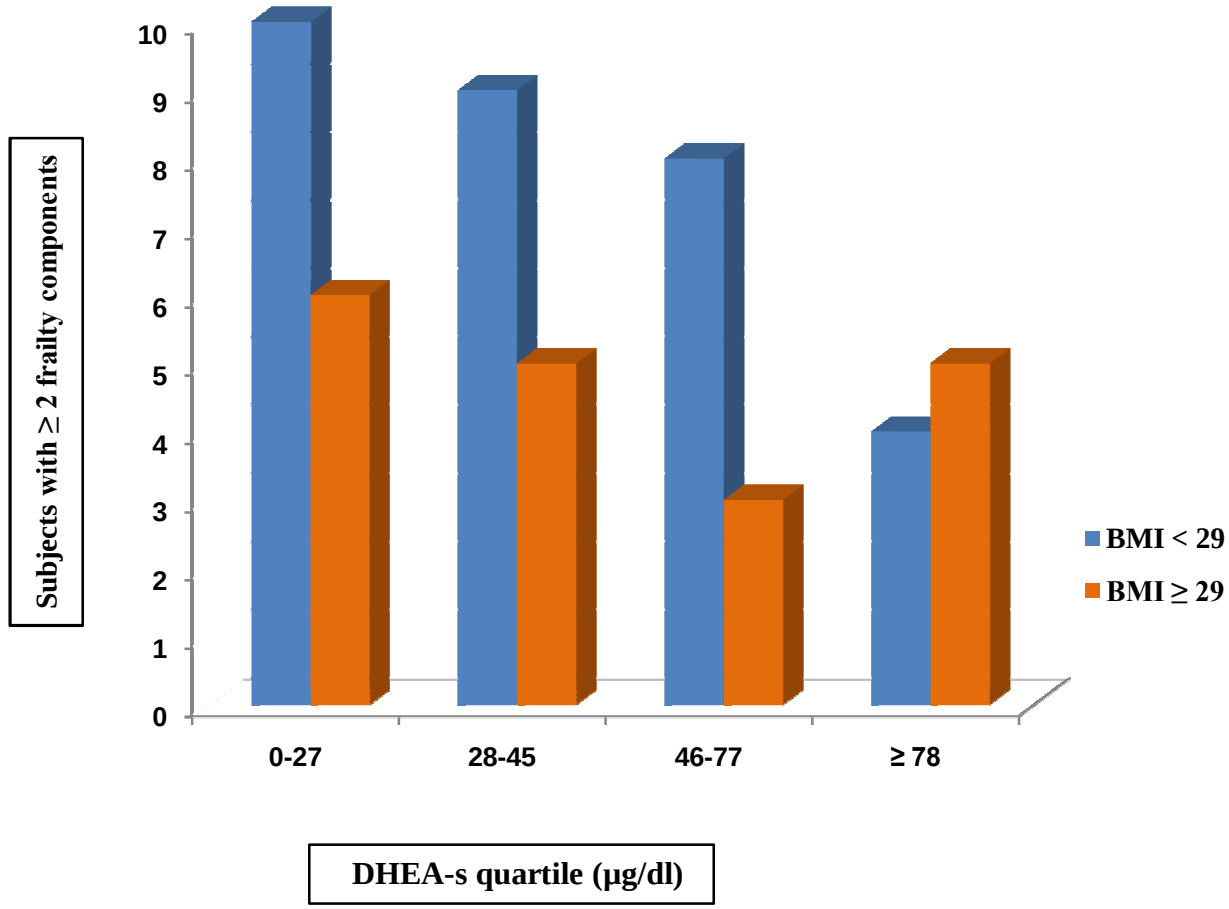
Chart 15 - **DHEA-BMI INTERACTION IN FRAIL INDIVIDUALS**



The relationship between higher levels of frailty decreased relative to higher levels of DHEA-s, but the magnitude of decrease was larger at lower BMI values and smaller at higher BMI values.

The relationship between being more frail decreased by a factor of 0.18 (95% CI 1.036, 1.379; **p = 0.02**) for every one unit increase in the DHEA-s level when BMI was ≤ 24 kg/m² (the lowest BMI quartile cut-off). In contrast, being more frail decreased only by a factor of 0.003 (95% CI 0.953, 1.055; **p = 0.92**) for every one unit increase in the DHEA-s level when BMI was ≥ 29 kg/m² (the highest BMI quartile cut-off). Having an intermediate BMI (24-29 kg/m²) resulted in an intermediate change by a factor of 0.08 (95% CI 0.797, 3.658; **p = 0.05**).

When the data were simultaneously cross-classified by frailty category, DHEA-s quartile and BMI level, the modifying effect of BMI on the association between frailty and DHEAS was evident. The graphical representation of the association suggested that there might be a threshold such that the inverse relationship between frailty and DHEA-s holds good for BMI values < 29 kg/m² and was weaker or absent for BMI values ≥ 29 kg/m².

The inverse relationship between DHEA-s and higher levels of frailty was strongest when BMI was < 29 kg/m² (OR =1.09, 95% CI 1.049, 1.139, **p = 0.0001**) and substantially weaker (OR = 0.82, 95% CI 0.953, 1.055; **p = 0.92**) when BMI exceeded 29 kg/m².

DISCUSSION

In this cross-sectional study of 100 elder men and women, we found that age, DHEA-s level and DHEAs-BMI interaction were associated with higher frailty categorization. We observed that an inverse association exists between DHEA-s level & frailty categories and the frailty phenotype increased with advancing age.

In a study conducted by Voznesensky et al[1], there were significant differences between categories of frailty across age ($p < 0.0001$), gender ($p = 0.0005$) and by DHEA-s levels ($p < 0.0001$). Our study noted significant difference across age ($p = 0.03$) and by DHEA-s levels ($p = 0.0004$) but did not observe any significant difference between the sexes ($p=0.97$). The mean age & DHEA-s level of the above study are 74.6 ±7.7 yrs & 59.2 ± 44.6 μg/dl respectively while the corresponding values for our study read 77.12 ± 6.79 yrs & 49.55 ± 24.97 μg/dl. Results of ordinal logistic regression model of both studies were comparable. With frailty as a dependent measure, both studies inferred that age, DHEA-s and interaction between DHEAs-BMI were predictive of more frailty characteristics.

In a study conducted by Leng et al[14], DHEA-s levels were lower among frail individual ($p < 0.02$). In another study conducted by Abbasi et al, men in the highest quartile of serum DHEA-s level were younger & more fit compared with those with a serum DHEA-s level in the lowest quartile. However no such

differences were identified between the women in the highest and the lowest quartiles of serum DHEA-s level.

In a study conducted by Paola Forti et al, low DHEA-s levels were associated with high degrees of self-rated disability[57]. In another study conducted by Berkman et al[15], high functioning among elders was found with those who have higher levels of DHEA-s.

In contrast, a cross-sectional study of 60 heart failure patients conducted by Boxer et al[18], failed to find an association between frailty and DHEA-s level.

In a study conducted by Lise Mazat et al., higher DHEA-s level was observed in subjects who had better mobility and physical performance. DHEA-s levels decreased significantly with increasing age in both sexes.

Several previous studies examined the relationship between DHEA-s and BMI with conflicting findings. Barrett-Connor and Ferrara[20], in a study of post-menopausal women, found DHEA-s levels to be directly associated with central obesity. Conversely, DHEA-s levels are inversely related with abdominal obesity or BMI >30 kg/m² in middle age and elderly men. Abbasi et al[17]., found DHEA-s to be positively correlated to BMI in women 60–80 years old, but not in men. Our study found a statistical significance between BMI and DHEA-s level as suggested by a p value of < 0.0001.

While the studies on the relationship between obesity and DHEA levels have been conflicting, frailty has been linked to higher BMI in a syndrome known as 'sarcopenic obesity'[27].

The association between frailty and a higher BMI may explain the attenuation of the association between DHEA-s and frailty at higher BMI. The mechanism may be direct. Sarcopenic obesity is associated with a decrease in strength and a decrease in mobility, two factors associated with frailty. The mechanism may also be indirect, as obesity is related to several biochemical markers associated with frailty, including elevated levels of inflammatory markers such as IL-6 and C-reactive protein and lower anti-oxidant capacity[28].

Blaum et al[29]., evaluated the association between obesity and frailty in elderly women and found that overweight (BMI 25–29.99 kg/m²) individuals were more likely to be classified as intermediate frail and obese individuals (BMI > 30 kg/m²) were more likely to be frail. We did not find a direct association between BMI and frailty, but did find an interaction between BMI and DHEA-s that was associated with frailty status. DHEA-s exhibited a protective effect against frailty in those with normal or overweight BMI, but the effect was lost in those with BMI > 30 kg/m² and may be explained by the biochemical markers associated with frailty, lower antioxidant capacity or the increased disabilities related to sarcopenic obesity.

In a study conducted by Fried LP et al[6]., frailty and age are found to be associated, with its incidence increasing from 3.2% of individuals aged 65–70 yrs to 25.7% of individuals aged 85–89 yrs. Our study too observed a significant association between the two variables ($p < 0.03$).

We found no gender interactions in the association between frailty and DHEA-s ($p=0.97$). Differences in DHEA-s levels between sexes have been described by Orentreich N et al[9]. Further, studies by Schaap LA et al[30]., have found an association between DHEA-s levels and physical performance in men, but not in women. While we found an association between frailty and DHEA-s levels, the association did not differ by gender.

In a study conducted by Ravaglia et al[60]., men with the highest functioning levels had the highest DHEA-s levels ($P < 0.03$). It suggested that DHEA-s levels may influence and/or be influenced by several endocrine and metabolic features of the oldest-old people, depending on the sexual steroid milieu. A favorable role for DHEA-s in successful aging is proposed.

LIMITATIONS OF THE STUDY

- The sample size is small (100 subjects).
- Whether the association between frailty and DHEA-s is due to similar conditions resulting in lower DHEA-s levels and more susceptibility to frailty or whether lower DHEA-s levels have an impact on increasing frailty cannot be addressed by this cross-sectional analysis.
- It does not address whether interventions to improve DHEA-s levels or modification in BMI will impact frailty status.

CONCLUSION

- The role of DHEA in frailty is uncertain, although low DHEA-s levels have been associated with increased rates of morbidity and mortality.
- In this cross-sectional analysis of 100 elder men and women, an inverse association was observed between the frailty categories and DHEA-s level. Higher DHEA-s levels were associated with fewer frailty characteristics.
- However, a BMI > 29 kg/m^2 attenuated the association found between DHEA-s level and frailty.
- With advancing age, the frailty phenotype increased.
- No gender interaction was observed in the association between frailty and DHEA-s level.
- Further research will need to be done to ascertain whether the association is due to similar conditions resulting in lower DHEA-s levels and more susceptibility to frailty or whether lower DHEA-s levels have an impact on increasing frailty.

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PROFORMA

A STUDY ON THE ASSOCIATION BETWEEN DEHYDROEPIANDROSTERONE AND FRAILTY IN ELDERLY

NAME: AGE:

SEX: OP / IP NO.:

ADDRESS: DATE:

Relevant History: H/O weight loss (10 lb in the past 1 year)

H/O exhaustion

H/O decrease in physical activity / grip strength / walking speed

Past History: H/O Diabetes Mellitus / Systemic Hypertension

H/O Adrenal tumour / insufficiency

H/O Prostate cancer

H/O Breast cancer

Drug History: DHEA / Estrogen / Androgen use in the preceding year

Anthropometry: Height- Weight- BMI-

FRAILTY ASSESSMENT COMPONENTS: **(FRIED'S CRITERIA)**

- 15 ft walking speed (in seconds):
- Physical activity (by Minnesota LTA questionnaire in kcal/wk):
- Handgrip strength (by Hand Dynamometer in kg):
- Weight loss (10 lb in the past 1 year): YES / NO
- Exhaustion: YES / NO

FRAILTY PHENOTYPE:

- NON-FRAIL (0 characteristic)
- INTERMEDIATE (1-2 characteristics)
- FRAIL ($\geq$ 3 characteristics)

SERUM DHEA-s LEVEL (μg/dl):

INFORMATION SHEET

TITLE: A STUDY ON THE ASSOCIATION BETWEEN DEHYDROEPIANDROSTERONE AND FRAILTY IN ELDERLY

NAME OF THE INVESTIGATOR: Dr. P.ARAVIND BABU
STUDY CENTRE: Rajiv Gandhi Government General Hospital, Chennai.
NAME OF THE PARTICIPANT: AGE: SEX:
PURPOSE OF THE STUDY: To evaluate the association between dehydroepiandrosterone (DHEA) and frailty in the elder population.
STUDY DESIGN: Observational study
STUDY PROCEDURE: We are selecting cases as per Fried's criteria and if you are found eligible, we may be using your blood sample (2 ml – only once) to measure serum DHEA which in any way does not affect your final report or management.
POSSIBLE RISKS: No possible risks by means of this study.
POSSIBLE BENEFITS: If this study confirms the association, therapeutic intervention by means of supplementation with DHEA can be considered.
CONFIDENTIALITY OF THE INFORMATION OBTAINED FROM THE PATIENT: The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
DECISION TO PARTICIPATE IN THE STUDY: Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
RESULT OF THE STUDY: The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date:
Place:

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு:சீரம் டிஹைட்ரோஎபிஆன்ட்ரோஸ்டீரோன் அளவை பலவீனமான முதியோர்களிடம் ஆராய்ந்து அறிதல்.

ஆராய்ச்சியாளர் பெயர்: மரு. பா.அரவிந்த் பாபு
ஆராய்ச்சி இடம்: ராஜீவ் காந்தி அரசு பொது மருத்துவமனை,சென்னை.
பங்கேற்பாளர் பெயர்: **வயது:** **பாலினம்:**

ஆராய்ச்சியின் நோக்கம்:

பலவீனமான முதியோர்களிடம் பிரச்சனைகள் பரவலாகக் காணப்படுகின்றன. முதியோர்கள் பலவீனமாவதற்கு பல்வேறு காரணங்கள் உண்டு, அதில் சீரம் டிஹைட்ரோஎபிஆன்ட்ரோஸ்டீரோன் குறைபாடும் ஒன்று. இந்த பரிசோதனை மூலம் இதை ஆராய்வதே இந்த ஆராய்ச்சியின் நோக்கம் ஆகும்.

ஆராய்ச்சி முறை:

இதில் உங்களுடைய உடம்பின் வலு சோதனை மற்றும் சீரம் டிஹைட்ரோஎபிஆன்ட்ரோஸ்டீரோன் அளவு போன்ற சிறப்பு பரிசோதனைகளைச் செய்து அதன் தகவல்களை ஆராய்வோம். பிரைடு கிரைடீரிய மூலம் முதியோர்களைத் தேர்வு செய்து அவர்களிடம் இருந்து 2 மி.லி. இரத்தம் மட்டும் ஒரு முறை எடுத்து சீரம் டிஹைட்ரோஎபிஆன்ட்ரோஸ்டீரோன் அளவை கண்டறிவதாகும்.

ஆராய்ச்சியின் பலன் மற்றும் தீங்கு:

இவற்றின் இடையேயான தொடர்பு உறுதிசெய்யப்பட்டால் டிஹைட்ரோஎபிஆன்ட்ரோஸ்டீரோனை மருந்தாக பின்னர் பயன் படுத்தவதற்கான நன்மை உருவாகலாம். இந்த ஆராய்ச்சியின் மூலம் பங்கேற்பவற்கு தீங்கேதும் கிடையாது. நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்கள் பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துகொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது அதன் முடிவில் அறிவிக்கப்படும் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இதனால் தங்களது ஆய்வறிக்கையோ, அன்றாட செயல்பாடுகளோ பாதிக்கப்படாது என்று தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள்:
இடம் :

PATIENT CONSENT FORM

Study Detail	:	**"A STUDY ON THE ASSOCIATION BETWEEN DEHYDROEPIANDROSTERONE AND FRAILTY IN ELDERLY"**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.	☐
b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.	☐
c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.	☐
d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.	☐
e) I hereby consent to participate in this study.	☐
f) I hereby give permission to undergo complete clinical examination and hematological tests.	☐

Signature/ thumb impression

Signature of the Investigator

Patient's Name & Address:

`

Study Investigator's Name

Dr. P.ARAVIND BABU

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு: சீரம் டிஹைட்ரோஎபிஆன்ட்ரோஸ்டீரோன் அளவை பலவீனமான முதியோர்களிடம் ஆராய்ந்து அறிதல்.
ஆராய்ச்சியாளர் பெயர்: மரு. பா.அரவிந்த் பாபு
ஆராய்ச்சி இடம்: ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை.
பங்கேற்பாளர் பெயர்: **வயது:**
பாலினம்: ஆண் / பெண்
அடையாள எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனது சீரம் டிஹைட்ரோஎபிஆன்ட்ரோஸ்டீரோன் அளவை பரிசோதனை செய்ய முழு சம்மதம்.

இந்த ஆராய்ச்சியில் யாருடைய நிர்பந்தமுமின்றி சொந்த விருப்பத்தின் பேரில் சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியில் இருந்து நான் எந்த நேரமும் பின் வாங்கலாம் என்றும், அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் புறிந்து கொண்டேன்.

நான் முதியோர் பலவீனம் குறித்த இந்த ஆராய்ச்சியின் விவரங்கள் கொண்ட தகவல்களை பெற்றுக்கொண்டேன்.

சீரம் டிஹைட்ரோஎபிஆன்ட்ரோஸ்டீரோன் பரிசோதனைக்கு, எனக்கு ஊசி மூலம் 2 மி.**லி** இரத்தம் ஒரு முறை மட்டும் எடுக்க சம்மதிக்கிறேன். இரத்தம் எடுக்கும் போது வலி, அரிப்பு, மயக்கம், போன்ற பின் விளைவுகள் ஏற்படலாம் என்று தெரிந்து கொண்டேன்.

நான் என்னுடைய சுய நினைவுடன் மற்றும் முழு சம்மதத்துடன் இந்த ஆராய்ச்சிக்கு என்னை பரிசோதிக்க சம்மதிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள்:
இடம்:

MASTER CHART

S.NO	AGE (yr)	SEX	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m²)	15 FT GAIT SPEED (sec)	GAIT SPEED (m/s)	PHYSICAL ACTIVITY LEVEL	HANDGRIP STRENGTH (Kg)	WEIGHT LOSS (>10% in 1 yr)	EXHAUSTION (self-reported)	NO. OF FRAILTY COMPONENTS	FRAILTY CATEGORY	DHEAs LEVEL (µg/dl)
1	67	MALE	165	65	23.88	5	0.91	HIGH	14	NO	NO	1	INTERMEDIATE	27.2
2	70	FEMALE	145	40	19.02	9	0.51	LOW	6	NO	YES	4	FRAIL	42.6
3	71	FEMALE	142	56	27.77	6	0.76	HIGH	8	NO	NO	1	INTERMEDIATE	24.6
4	76	MALE	152	42.5	18.40	5	0.91	LOW	12	NO	YES	3	FRAIL	20.3
5	78	FEMALE	148	45	20.54	9	0.51	LOW	3	YES	YES	5	FRAIL	19.8
6	80	MALE	160	60	23.44	5	0.91	HIGH	9	NO	NO	1	INTERMEDIATE	16.7
7	66	MALE	167	82	29.40	5	0.91	HIGH	33	NO	NO	0	NON-FRAIL	26.7
8	72	FEMALE	144	45	21.70	9	0.51	LOW	2	YES	YES	5	FRAIL	23.4
9	82	FEMALE	148	52	23.74	10	0.46	LOW	9	NO	NO	3	FRAIL	22.6
10	67	MALE	165	64	23.51	5	0.91	HIGH	13	NO	NO	1	INTERMEDIATE	26.9
11	73	FEMALE	144	57	27.49	8	0.57	HIGH	22	NO	NO	1	INTERMEDIATE	23.7
12	71	MALE	165	63	23.14	6	0.76	HIGH	30	NO	NO	0	NON-FRAIL	37.8
13	76	FEMALE	146	59	27.68	6	0.76	HIGH	7	NO	YES	2	INTERMEDIATE	22.6
14	79	MALE	170	67	23.18	5	0.91	HIGH	30	NO	NO	0	NON-FRAIL	33.5
15	82	MALE	152	47	20.34	10	0.46	LOW	6	YES	YES	5	FRAIL	17.5
16	79	FEMALE	145	65	30.92	11	0.42	LOW	5	NO	YES	4	FRAIL	18.6
17	86	FEMALE	144	45	21.70	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	25.7
18	80	MALE	150	50	22.22	9	0.51	LOW	13	NO	YES	4	FRAIL	30.4
19	85	MALE	164	63.5	23.61	5	0.91	HIGH	9	NO	NO	1	INTERMEDIATE	30.3
20	87	FEMALE	140	38	19.39	10	0.46	LOW	4	NO	NO	3	FRAIL	15
21	68	MALE	162	62	23.62	5	0.91	HIGH	14	NO	NO	1	INTERMEDIATE	45.6
22	82	FEMALE	157	62	25.15	9	0.51	HIGH	6	NO	NO	2	INTERMEDIATE	28.9
23	72	FEMALE	154	54	22.77	8	0.57	LOW	3	YES	YES	5	FRAIL	23.9
24	79	FEMALE	156	52	21.37	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	23.9
25	69	FEMALE	155	49	20.40	6	0.76	HIGH	19	NO	NO	0	NON-FRAIL	30.8

26	80	MALE	165	55	20.20	5	0.91	LOW	11	NO	YES	3	FRAIL	16.6
27	82	FEMALE	150	58	25.78	9	0.51	LOW	8	YES	YES	4	FRAIL	60.6
28	70	FEMALE	153	56	23.92	6	0.76	HIGH	20	NO	NO	0	NON-FRAIL	32.9
29	83	FEMALE	148	68	31.04	6	0.76	HIGH	9	NO	NO	1	INTERMEDIATE	27.9
30	74	MALE	163	57	21.45	10	0.46	LOW	14	NO	YES	4	FRAIL	16.4
31	69	FEMALE	145	47	22.35	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	56.7
32	81	FEMALE	154	58	24.46	9	0.51	LOW	2	YES	YES	5	FRAIL	64.8
33	76	FEMALE	155	57.5	23.93	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	49.8
34	73	MALE	155	72	29.97	9	0.51	LOW	12	NO	YES	4	FRAIL	43.5
35	68	FEMALE	155	59	24.56	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	65.7
36	85	FEMALE	147	56	25.92	11	0.42	LOW	1	YES	YES	5	FRAIL	80.5
37	82	MALE	156	60	24.65	10	0.46	LOW	8	YES	YES	5	FRAIL	15.5
38	78	FEMALE	145	58	27.59	9	0.51	HIGH	22	NO	NO	1	INTERMEDIATE	30.5
39	86	MALE	150	58	25.78	5	0.91	LOW	8	NO	YES	3	FRAIL	15
40	87	MALE	153	50	21.36	10	0.46	LOW	6	YES	YES	5	FRAIL	16.5
41	71	MALE	156	72	29.59	5	0.91	HIGH	16	NO	NO	1	INTERMEDIATE	38.9
42	70	FEMALE	153	59	25.20	9	0.51	LOW	9	NO	NO	3	FRAIL	45.8
43	82	FEMALE	154	58	24.46	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	78.9
44	68	MALE	165	80	29.38	5	0.91	HIGH	33	NO	NO	0	NON-FRAIL	40.8
45	78	MALE	160	60	23.44	8	0.57	HIGH	30	NO	NO	1	INTERMEDIATE	34.9
46	77	FEMALE	154	55	23.19	6	0.76	HIGH	7	NO	YES	2	INTERMEDIATE	31.7
47	66	FEMALE	154	58.5	24.67	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	83.8
48	80	MALE	160	62	24.22	9	0.51	HIGH	12	NO	NO	2	INTERMEDIATE	29.8
49	67	MALE	165	63	23.14	5	0.91	HIGH	30	NO	NO	0	NON-FRAIL	68.9
50	70	FEMALE	152	54	23.37	6	0.76	LOW	8	NO	NO	2	INTERMEDIATE	64.6
51	78	MALE	160	62	24.22	5	0.91	HIGH	15	NO	NO	1	INTERMEDIATE	32.3
52	68	FEMALE	150	52	23.11	6	0.76	HIGH	21	YES	YES	2	INTERMEDIATE	40.9
53	80	MALE	167	65	23.31	5	0.91	HIGH	30	NO	NO	0	NON-FRAIL	34.9
54	82	MALE	153	57	24.35	9	0.51	LOW	7	YES	YES	5	FRAIL	18.8

55	90	MALE	152	59	25.54	10	0.46	LOW	8	NO	YES	4	FRAIL	52.4
56	69	FEMALE	158	60	24.03	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	85.6
57	89	MALE	148	56	25.57	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	78.8
58	78	MALE	156	63	25.89	9	0.51	LOW	5	YES	YES	5	FRAIL	57.9
59	77	FEMALE	145	45	21.40	6	0.76	HIGH	10	NO	NO	1	INTERMEDIATE	48.9
60	92	FEMALE	143	60	29.34	12	0.38	LOW	8	NO	YES	4	FRAIL	15.2
61	67	FEMALE	148	56	25.57	6	0.76	HIGH	19	NO	NO	0	NON-FRAIL	84.5
62	68	MALE	160	65	25.39	10	0.46	LOW	10	NO	NO	3	FRAIL	25.5
63	77	FEMALE	150	67	29.78	9	0.51	LOW	9	NO	NO	3	FRAIL	83.9
64	80	MALE	152	58	25.10	5	0.91	HIGH	13	NO	NO	1	INTERMEDIATE	48.7
65	76	MALE	165	79.5	29.20	5	0.91	HIGH	33	NO	NO	0	NON-FRAIL	67.9
66	78	MALE	159	63	24.92	8	0.57	HIGH	10	NO	NO	2	INTERMEDIATE	54.7
67	68	MALE	168	60	21.26	5	0.91	HIGH	30	NO	NO	0	NON-FRAIL	75.6
68	86	MALE	155	70	29.14	8	0.57	LOW	6	NO	NO	3	FRAIL	29.5
69	85	MALE	145	52	24.73	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	79.8
70	86	MALE	156	72	29.59	9	0.51	LOW	13	NO	YES	4	FRAIL	59.9
71	68	MALE	164	63	23.42	5	0.91	HIGH	30	NO	NO	0	NON-FRAIL	77.6
72	78	FEMALE	150	46	20.44	9	0.51	HIGH	22	NO	NO	1	INTERMEDIATE	52.3
73	69	FEMALE	142	56	27.77	6	0.76	HIGH	9	NO	YES	2	INTERMEDIATE	84.5
74	80	MALE	158	62	24.84	5	0.91	HIGH	7	NO	YES	2	INTERMEDIATE	49.7
75	70	MALE	162	65	24.77	5	0.91	HIGH	8	YES	NO	2	INTERMEDIATE	65.9
76	83	MALE	161	58	22.38	5	0.91	HIGH	30	NO	NO	0	NON-FRAIL	60.9
77	82	MALE	158	61	24.44	9	0.51	HIGH	9	NO	NO	2	INTERMEDIATE	47.2
78	79	FEMALE	150	44	19.56	6	0.76	LOW	8	NO	YES	3	FRAIL	35.5
79	81	MALE	160	67	26.17	5	0.91	LOW	8	NO	NO	2	INTERMEDIATE	82.8
80	88	MALE	161	68	26.23	10	0.46	HIGH	5	NO	NO	2	INTERMEDIATE	78.8
81	73	MALE	165	68	24.98	5	0.91	HIGH	31	NO	NO	0	NON-FRAIL	84.5
82	68	MALE	168	72	25.51	5	0.91	HIGH	31	NO	NO	0	NON-FRAIL	87.6
83	67	FEMALE	146	60	28.15	6	0.76	HIGH	10	NO	NO	1	INTERMEDIATE	87.8

84	84	FEMALE	155	70.5	29.34	6	0.76	HIGH	22	NO	NO	0	NON-FRAIL	78.9
85	80	MALE	167	67.5	24.20	5	0.91	HIGH	31	NO	NO	0	NON-FRAIL	80.5
86	78	FEMALE	144	56	27.01	6	0.76	HIGH	22	NO	YES	1	INTERMEDIATE	49.8
87	82	MALE	163	69.5	26.16	5	0.91	HIGH	31	NO	NO	0	NON-FRAIL	80.9
88	87	FEMALE	145	66	31.39	10	0.46	LOW	4	NO	YES	4	FRAIL	16.4
89	85	MALE	155	71	29.55	9	0.51	LOW	9	NO	YES	4	FRAIL	80.9
90	68	MALE	158	73	29.24	5	0.91	LOW	9	NO	NO	2	INTERMEDIATE	89.8
91	77	MALE	156	71.5	29.38	9	0.51	HIGH	9	NO	NO	2	INTERMEDIATE	85.6
92	78	MALE	165	67	24.61	5	0.91	HIGH	31	NO	NO	0	NON-FRAIL	83.4
93	69	MALE	169	70.5	24.68	5	0.91	HIGH	31	NO	NO	0	NON-FRAIL	86.7
94	86	FEMALE	148	67	30.59	9	0.51	LOW	5	NO	YES	4	FRAIL	29.5
95	82	FEMALE	162	63.5	24.20	5	0.91	HIGH	31	NO	NO	0	NON-FRAIL	83.2
96	80	FEMALE	165	67.5	24.79	5	0.91	HIGH	31	NO	NO	0	NON-FRAIL	78.6
97	73	FEMALE	157	59.5	24.14	6	0.76	HIGH	18	NO	NO	0	NON-FRAIL	80.2
98	86	FEMALE	155	73	30.39	6	0.76	HIGH	6	NO	YES	2	INTERMEDIATE	47.2
99	72	MALE	156	72	29.59	9	0.51	LOW	10	NO	NO	3	FRAIL	82.5
100	85	FEMALE	154	72.5	30.57	9	0.51	HIGH	4	NO	NO	2	INTERMEDIATE	79.8